

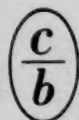
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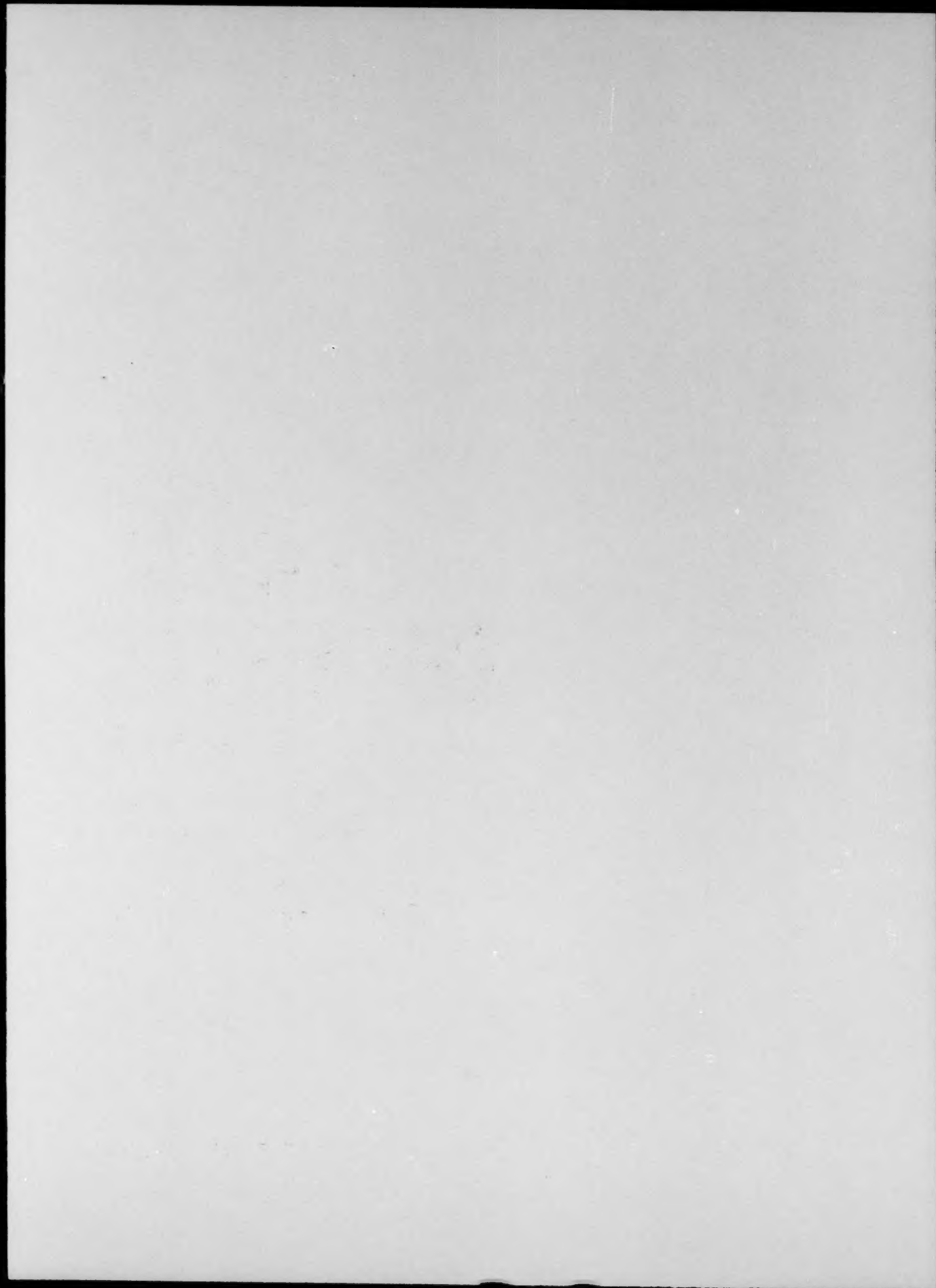
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(ZHURNAL OBSHCHEI KHIMII)

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IN MEMORY OF ACADEMICIAN NIKOLAI DMITRIEVICH ZELINSKII

(ON THE HUNDREDTH ANNIVERSARY OF HIS BIRTH)

N. I. Shuikin

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February 6, 1961 marks the hundredth anniversary of the birth of Academician Nikolai Dmitrievich Zelinskii — professor at the Moscow State University, tutor and head of the major Soviet school of organic chemists, founder of the science of catalytic transformations, inventor of the first universal gas mask.

Having obtained his education in the natural sciences at Novorossiisk (Odessa) University, and then for a number of years abroad (Leipzig, Göttingen), Nikolai Dmitrievich up to 1893 conducted pedagogical and scientific research work in the field of organic chemistry at Novorossiisk University, where he completed and brilliantly defended his Master's (1889) and Doctor's (1891) theses.

Personal contact with his famous teachers (A. A. Verigo, P. G. Melikishvili, I. M. Sechenov, I. I. Mechnikov, O. A. Kovalevskii, J. Wislicenus, V. Meyer), and later his association with the leaders of Russian progressive natural science (K. A. Timiryazev, N. A. Umov, P. N. Lebedev, A. G. Stoletov, I. P. Pavlov), exerted a decisive influence on the molding of the materialistic world outlook of N. D. Zelinskii — naturalist with a broad range of scientific interests.

Beginning with the second half of 1893 and up to his death on July 31, 1953, Nikolai Dmitrievich conducted scientific and pedagogical work at the Moscow State University, where up to 1930 he headed the combined Departments of Organic and Analytical Chemistry, and then — up to the last days of his life — the Department of Petroleum Chemistry. Together with this, N. D. directed a major section of the Institute of Organic Chemistry of the Academy of Sciences of the USSR, composed of the laboratories: Kinetics of Catalytic Organic Reactions, Catalytic Synthesis, and Organic Catalysis; and he also directed a section in the Petroleum Institute of the Academy of Sciences of the USSR. In addition, N. D. was co-director with L. F. Vereshchagin in the Institute of Organic Chemistry of the Academy of Sciences of the USSR of the Ultrahigh Pressure Laboratory, created on his initiative.

The main directions of the vast and actual scientific research work of N. D. Zelinskii are the synthesis and catalytic-contact transformations of hydrocarbons, the chemistry of petroleum, organic catalysis and the development of scientific foundations for selecting hydrogenation and dehydrogenation catalysts, and also the chemistry of proteins. In collaboration with his students and co-workers he published approximately 600 scientific papers. Mention should be made of the distinguished studies of N. D. on the cracking of petroleum hydrocarbons on natural aluminosilicates and synthetic oxide catalysts, preceding the E. Houdry patent by more than 20 years [1, 2].

On the basis of his experimental studies and theoretical concepts, N. D. at the height of the First World War invented the first universal carbon gas mask, which in 1916 was adopted to outfit the Russian army and saved the lives and health of tens of thousands of Russian soldiers [3-5]. Mention should also be made of the very important applications of the fundamental studies of N. D. Zelinskii and his school in the production of modern high-test aviation fuel and in the industrial catalytic synthesis of pure aromatic hydrocarbons from petroleum [6-9], and also of his penetrating investigations on the chemical structure of albumin [10].

We are not gathered here to discuss the content of the distinguished studies of N. D. Zelinskii, since this has been done many times, the last time in 1951, in connection with the 90-Year Jubilee of N. D. [11, 12]. Just a listing of his original studies would take up too much time and space. It is only desired to especially emphasize that in all of his scientific achievements he was motivated by a patriotic duty to his glorious Fatherland — in close association with his numerous students, whom he solicitously trained in the spirit of the best traditions of leading Soviet science, and whom he loved with a fatherly love.

In the process of the creative and purposeful development of very important subdivisions of chemical science and its applications, N. D. created the topmost major school of organic chemists in our country. Together with this, many generations of young chemists obtained the creative spark and a deep knowledge of organic chemistry at the outstanding and inspired lectures and in the laboratories of N. D. Zelinskii during the 60 years of his scientific and pedagogical activities at the Moscow State University.

It is difficult to find in the Soviet Union an institution of higher chemical learning, a chemical scientific research institute or a major chemical plant where students of N. D. or students of his co-workers and students are not working. During the entire time of its development this school, encouraged and developed in the best traditions of the progressive Soviet intelligentsia, has represented an efficient and creative collective; chief N. A. Zelinskii was himself its authoritative director, consultant, strict critic, sincere well-wisher and friend.

Even in the first, the Odessa, period of his scientific and pedagogical activity N. D. was able to collect around himself and train a large number of talented students, among whom mention should be made of A. M. Bezredk, A. A. Bychikhin, S. G. Krapivin, A. G. Doroshevskii, and others.

The brilliant scientific, pedagogical and organizing activity of N. D. at the Moscow University can be judged just from the fact that up to 1916 more than twenty of his students of this first period subsequently became professors in the chemical departments of various institutions of higher learning in our country. Among them should be mentioned such famous names as L. A. Chugaev, A. N. Reformatskii, N. A. Shilov, S. N. Naumov, E. S. Przheval'skii, A. N. Lebedev, N. A. Rozanov, A. E. Uspenskii, I. V. Kulikov, V. V. Longinov, N. A. Glinka, I. F. Gutt, A. E. Mozer, N. A. Shlezinger, S. S. Namekin, B. M. Berkengeim, A. V. Rakovskii, N. A. Izgaryshev, V. V. Chelintsev, and a number of other major chemists.

Commencing after the victory of the Great October Socialistic Revolution, the second or Moscow period of the scientific-pedagogical and public activity of N. D. Zelinskii, embracing more than three decades, is extremely fruitful, being highly saturated with studies of major theoretical and national economy importance. In this Soviet period the school of N. D. Zelinskii raised a whole new order of scientists, recommending themselves as major investigators. This new order of students of N. D. includes Academicians A. N. Nesmeyanov, A. A. Balandin and B. A. Kazanskii, Corresponding Members of the Academy of Sciences of the USSR K. A. Kocheshkov, K. P. Lavrovskii, Yu. G. Mamedaliev, A. P. Terent'ev and N. I. Shuikin, Doctors of Chemical Sciences and Professors Yu. A. Arbuzov, P. P. Borisov, N. I. Gavrilov, G. D. Gal'pern, Ya. I. Denisenko, E. D. Kaverzneva, N. S. Kozlov, R. Ya. Levina, B. V. Maksorov, B. M. Mikhailov, S. S. Novikov, G. S. Pavlov, A. F. Platé, A. M. Rubinshtein, V. S. Sadikov, M. B. Turova, M. I. Ushakov, Ya. T. Éidus and Yu. K. Yur'ev, and a large group of tutors, working as chemical science candidates.

As a result, we see that together with solving the more important problems in the development of science and practice, N. D. fulfilled with foresight and diligence the esteemed task of training highly qualified research chemists, possessing the knowledge and the research of pedagogical study. He always assigned exclusively great importance to this important problem of training future scientists at all stages of preparation. His grateful students hold holy the bright memory of their teacher. The greatest memorial to N. D. Zelinskii is a further creative development of his school. After the death of their eminent leader his school continues to live a full-blooded life, and together with an expansion and deeper investigation of the basic ideas of N. D. on the basis of contemporary achievements in the natural sciences, it creates new original directions of scientific study. Of necessity we will attempt to refer briefly to the more important scientific advances made by the students of N. D. Zelinskii.

The Soviet school of the chemistry of organometallic compounds, created and directed by A. N. Nesmeyanov, owes its start to the early distinguished researches conducted in the laboratory of N. D. Zelinskii at the Moscow State University, where A. N. Nesmeyanov discovered and developed the reaction known as the diazo method of synthesizing organometallic compounds. In the laboratories of the Institute of Organic Chemistry of the Academy of Sciences of the USSR, Moscow State University, and the Institute of Heteroorganic Compounds of the Academy of Sciences of the USSR the researches of A. N. Nesmeyanov and his students and co-workers led to the development of the principles of the synthesis, chemical transformations and reactivity of many organometallic compounds, but their greatest contribution was made in the field of the chemistry of the organomercury and organoiron compounds and of metal carbonyls and in the development, together with R. Kh. Freidlina, of the so-called telomerization reaction of olefins with carbon tetrachloride, leading to the synthesis of very important amino acids, serving as raw material for the manufacture of synthetic fibers. This school is famous far beyond the boundaries of the USSR. In



Academician Nikolai Dmitrievich Zelinskii
(1861-1953)

the last decade this school has found further development and at the present time embraces the chemistry of hetero-organic compounds, with which material A. N. Nesmeyanov and his students and co-workers (M. I. Kabachnik, R. Kh. Freidlin, O. A. Peutov, N. K. Kochetkov, and others) are conducting important investigations in the domain of the further development of the theory of chemical structure and reactivity of organic compounds.

In the chemistry of organometallic compounds a major contribution has been made by another student of N. D. Zelinskii, namely K. A. Kocheshkov, who in collaboration with his students is doing brilliant work in developing the broad fields of organotin, -lead and -lithium compounds.

A. A. Balandin on the material of N. D. Zelinskii's studies in the field of the dehydrogenation of hydrocarbons and on the basis of his own investigations has extensively developed and improved the multiplet theory of catalysis by introducing into it the principle of energetic conformity and the finding of the values of the bond energies for a number of organogens with metals (in collaboration with A. A. Tolstopyatova, S. Kiperman, and others). Some of the investigations, started even jointly with N. D., he carried clear up to the stage of industrial utilization, for example, such actual processes as the dehydrogenation of the butenes to butadiene, of the pentenes to isoprene (jointly with O. K. Bogdanova and A. P. Shegeglova), and of diethylbenzene to divinylbenzene (jointly with G. M. Marukyan). In company with G. M. Marukyan he also worked out the reactions for the catalytic dehydrogenation of α -ethylthiophene to α -vinylthiophene and of ethylpyridine to vinylpyridine. Acting as scientific leader of three major groups of scientists in the Academy of Sciences of the USSR and Moscow State University, A. A. Balandin created a school of catalytic chemistry, successfully working out a number of important theoretical problems and processes of great importance to the national economy. The researches of L. Kh. Freidlin and co-workers are of great interest in the field of the selective catalytic hydrogenation of organic compounds in the liquid phase under pressure. Chief consideration in his studies is given to the chemical mechanism of reactions and the mechanism of their activation.

B. A. Kazanskii widely expanded the research started by him jointly with N. D. Zelinskii in the field of the catalytic hydrogenolysis of the pentamethylene ring. In collaboration with A. F. Platé and other co-workers he developed very important rules pertaining to opening of the ring of various cyclopentane homologs in the presence of a series of catalysts in a hydrogen atmosphere. He in association with a large group of co-workers made a detailed study of the dehydrocyclization of individual alkanes and their mixtures (in gasolines) on various catalysts. In the plane of the main directions of N. D. Zelinskii's school, a very interesting reaction of the ring closure of certain alkanes with the formation of a five-membered ring when using a platinized active carbon catalyst was recently discovered by B. A. Kazanskii and A. L. Liberman. At the present time researches in this direction are being successfully pursued. In the Laboratory of Catalytic Synthesis of the Institute of Organic Chemistry of the Academy of Sciences of the USSR, headed by B. A. Kazanskii, a number of other important investigations are being carried out, owing their origin to the general line of N. D. Zelinskii's studies. Here mention should first be made of the development by B. A. Kazanskii in collaboration with G. S. Landsberg, A. F. Platé and a group of co-workers of a combined method of investigating the individual composition of straight run gasolines, currently used in the petroleum refining industry. Supplementing what has just been said, mention should also be made of the researches with M. Yu. Lukina on the synthesis and elucidation of the rules governing ring opening in the series of cyclopropane and cyclobutane hydrocarbons, the investigations of Ya. T. Eidus in the field of the catalytic hydrocondensation of alkenes with carbon monoxide, the studies of A. F. Platé on the synthesis of unsaturated cyclic systems from cyclopentadiene and acetylene, and the investigations of M. G. Gonikberg in the field of the thermal transformations of various classes of hydrocarbons at ultrahigh pressures.

N. I. Shuikin in collaboration with Kh. M. Minachev and other co-workers developed the classic studies of N. D. Zelinskii on dehydrogenation catalysis in the direction of investigating the transformations of various classes of hydrocarbons under hydrogen pressure and at high temperatures on the Group VIII metals of the periodic system. As a result of this work basic rules were developed for the contact-catalyzed transformations of hydrocarbons on low-grade catalysts, and the principles of the catalytic reforming of gasolines in order to improve them were worked out. N. I. Shuikin in company with T. I. Naryshkina successfully worked out the reaction for the catalytic dehydrogenation of five-membered cyclenes and cyclanes to the corresponding cyclopentadienes. In collaboration with I. F. Bel'skii, N. I. Shuikin also originated and successfully worked out a new direction in the chemistry of furan compounds, namely investigations of the rules governing the selective catalytic hydrogenolysis of the furan ring in various furan derivatives. The results of these investigations led to establishing new paths for the catalytic synthesis of difficultly available aliphatic ketones and diketones, and also of alkylcyclohexanones and individual homologs of phenol from furfural. The found rules enabled the authors to work out in principle new methods for the synthesis of dialkyl- and trialkyltetrahydrofurans and of amines of the furan series and their conversion in high yields to pyrrolidine homologs. Recently

N. I. Shuikin in company with N. G. Bekauri discovered a new reaction for the catalytic polycyclization of the higher alkanes to condensed phenanthrene, anthracene, chrysene and benzantracene systems and other more complex polycycles. On the basis of this reaction they worked out an original method for the catalytic reforming of kerosene with the formation of a new luminescent testing liquid "shubekol", used in a number of machinery plants for spotting defects in important metallic and nonmetallic articles and parts.

Valuable contribution to the development of the chemistry of hydrocarbons has been made by R. Ya. Levina at the Moscow University. In association with co-workers, she has developed new methods for the synthesis of alkanes and cyclanes with one, two and three quaternary carbon atoms in the side chain. On the basis of the discovered reaction for the catalytic decomposition of tetrahydropyridazines she proposed a method for the synthesis of arylcyclobutanes, while another reaction discovered by R. Ya. Levina — the aromatization of tetrahydrophthalic anhydrides — proved to be a general method for the synthesis of aromatic hydrocarbons in the benzene, naphthalene, indan, phenanthrene, chrysene and fluorene series, and of their partially hydrogenated derivatives. These investigations in turn led to the discovery of the reaction for the cleavage of the three-membered ring with mercury salts, showing a close analogy in the properties of the three-membered ring and the double bond. Study of the chemical and physical properties of arylcyclopropanes and arylcyclobutanes enabled R. Ya. Levina and co-workers to establish the presence of conjugation between the benzene ring and a three-membered cycle, and also a four-membered cycle, although less clearly expressed in the latter case.

The studies of K. P. Lavrovskii are of great scientific and practical interest in the field of developing the principles of the technology of fuels, leading to the creation of new processes for the production of high-grade gasolines. Together with co-workers, K. P. Lavrovskii worked out a process for the high-speed cracking of heavy petroleum fractions, giving a high yield of olefins — a valuable raw material in the production of various high-molecular compounds.

Researches on the alkylation and chlorination of hydrocarbons are being conducted on a wide front by Yu. G. Mamedaliev and a large group of co-workers in Baku. The principal results of these investigations have already been introduced into the petroleum refining industry. The original investigations of Yu. G. Mamedaliev on the production of chlorinated hydrocarbons are of great interest.

The investigations of Yu. K. Yur'ev and co-workers in the field of the chemistry of heterocyclic compounds have attained wide scope at the Moscow University. Yu. K. Yur'ev, discovering the reaction of the catalytic transformation of heterocycles, made successful use of it to synthesize standards of cyclic sulfides, and also for the catalytic conversion of furanidine (tetrahydrofuran) and tetrahydropyran to the corresponding silicon-containing heterocycles. Yu. K. Yur'ev and co-workers proposed a convenient method for the synthesis of ketones and keto acids of the furan, pyrrole, thiophene and selenophene series, and also of benzene, by the acylation of tetraacyloxy- and acyloxytrichlorosilanes, and he was the first to make a broad and detailed study of the chemistry of selenophene, describe methods for the synthesis of various compounds of the furan series, establish the rules of the diene synthesis and the reactions of substitutive addition in the furan series, make a comprehensive study of the reactivity of ketones and α -diketones of the tetrahydrofuran series, and accomplish their conversion to mono- and diketones of the tetrahydropyran series.

The researches of N. I. Gavrilov, M. M. Borvinik, E. D. Kaverzneva, K. T. Poroshin, A. B. Silaev, M. A. Prokof'ev, and E. A. Morozova and co-workers led to further creative developments in the domain of establishing the micro-molecular structure of proteins, the synthesis of hydroxyamino acids, and the establishment of the optimum conditions for the hydrolysis of proteins and a detailed study of the composition of the hydrolyzates. These studies greatly expanded our concepts regarding the possible structure of protein molecules.

Within the frame of the present paper it is impossible to even schematically outline the successes of still many other students of N. D. Zelinskii, engaged in developing his creative ideas. For this reason we have omitted mention here of the superlative investigations of A. P. Terent'ev and his students in the domain of the synthesis of physiologically active organic compounds, the interesting investigations of M. B. Turova-Polyak in the domain of catalytic alkylation, the studies of A. M. Rubinshtein in the domain of the physicochemical investigation of catalysts, the outstanding investigations of S. R. Sergienko in the domain of the chemistry of high-molecular hydrocarbons, the work of B. M. Mikhailov on the synthesis of organoboron compounds and study of their properties, of N. S. Kozlov on the synthesis of amines, of Yu. A. Arbuzov in the domain of the diene synthesis based on the nitroso derivatives of aromatic hydrocarbons, of L. F. Vereshchagin in the domain of the chemistry and physics of ultrahigh pressures, of I. N. Tits-Skvortsova in investigation of catalytic transformation of organic sulfur compounds, and of P. P. Borisov in the domain of the oxidation of oils and individual hydrocarbons.

To judge the vast scale of the developments of the school of N. D. Zelinskii it is necessary to keep in mind that a number of his close students molded their own students into independent investigators, actively pursuing scientific research work in directions—the sources of which lie in the ideas and initiations of N. D. Zelinskii. Many of these "chemical grandchildren" of N. D. have at the present time defended their Candidatal and Doctoral dissertations, while some of them are members of the Academy of Sciences or conduct leading work in the chemical and petroleum-refining industries.

It should be mentioned that N. D. was always a firm adherent of the broad education of chemists in the natural sciences. Fully realizing the need and practicality of specialization, in connection with the differentiation of the scientific disciplines, he always remained an opponent to the narrow specialization of scientists. Actually, the modern development of science, even in separate, special sections, for a deep understanding requires from the investigator a broad view and also a knowledge of contiguous disciplines. Only with a complete mutual understanding can separate groups of scientists of different specializations, in close coordination, successfully solve the maturing theoretical questions of science and the problems of major importance to the national economy. Even in 1922, in the final speech at the close of the Third Mendeleev Convention, N. D. Zelinskii said: "The most important and basic problems of our concepts regarding Nature require a mutual solution; here it is necessary to involve mathematics, mechanics, physics, chemistry, biology, bacteriology, medicine, mineralogy, geology and even astronomy, for the microcosmos of chemical molecules and the structure of atoms cannot help but reflect in themselves the elements of the structure of the universe".

Wherein lay the essence of the approach of N. D. to the training of future scientists and what were the conditions assuring a high level and a broad scope of preparation of the chemists trained under his guidance? In reply to these questions it would first be necessary to enumerate a whole series of outstanding traits, characterizing N. D. not only as a major scientist of world renown and a prominent social worker, but also as an appreciative, sympathetic man. This personal charm, coupled with a firm scientific authority, theoretical exactions on himself and his students, persistence, and an amazing capacity for work always attracted talented youth to N. D., deciding to devote themselves to the service of science. In his memoirs of N. D. Zelinskii, the late Academician V. M. Rodionov wrote in 1951 [13]: "He was always original in his arguments, listened attentively to strange opinions, loved debates, and became irate, more truly vexed, but only when his opponent permitted himself gross inconsistencies. He himself was very correct, which never, however, prevented him from stoutly defending his position".

As a result, the personal example of the teacher in daily creative work, a systematic mixing with the students in this creative work, a constant opposing of the minds in the course of an open discussion of his ideas and new plans in individual discussions and at colloquiums, in instilling of a live initiative in his co-workers — this is what attracted a stream of students and followers to the great leader. There was no need for such a genuine head of the school to seek capable, serious students; they themselves strived to be worthy of the honor of doing work with N. D. Zelinskii.

In his creative and educational work N. D. carried one fundamental thought: "A genuine scientist can be one who possesses enthusiasm and passion toward science and its applications. A scientist should dedicate his entire life to the supreme service of the people. Loyalty to science and devotion to the Socialistic Republic — this should be the motto of the scientist, if he truly wants to exalt the fame of the Russian scientific thought".

As a true patriot, N. D. performed major and responsible public work. Without exaggeration it can be said that in the ranks of the older generation of scientists he was one of the most prominent public workers. Even in the czarist regime he stood out as a progressive worker of the higher school. Advocate of higher education for women, he toward the end of the nineties of the past century organized the department of organic chemistry in the just opened Higher Women's Courses in Moscow and was its first director. N. D. was an active participant in the organization of the Shanyavskii Public University in Moscow. From 1893 N. D. took a working part in the researches of the Moscow Society of Investigators of Nature, oldest in the country. In 1921 he was honored with the title of Esteemed Member of this society, while from 1935 on he was elected to be its president. Beginning with the 90's of the past century N. D. took an active part in the activities of the Society of Amateurs in the Natural Sciences, Anthropology and Ethnography, and especially of the Russian Physical-Chemical Society. From 1934 he conducted leading research in the D. I. Mendeleev All-Union Chemical Society, which succeeded the Russian Physical-Chemical Society. And also here he was honored with the title of Esteemed Member of the Society.

The scientific and pedagogical activity of N. D. is a shining example of innovation in science. He had to the highest degree a sense of the new, which is a powerful impellent of progress. Predicting a great importance for

radioactive radiations in scientific studies, N. D. even in 1922 studied the action of radium rays on hydrocarbons. The results of this work were presented by him at the Third Mendeleev Convention [14]. Assigning a very great importance to the use by research chemists of modern physical methods, N. D. (jointly with G. S. Landsberg and B. A. Kazanskii) devised for the detailed analysis of gasoline an original method of investigating hydrocarbons by means of Raman spectra, giving (in conjunction with catalysis, chromatographic adsorption and precise fractional distillation) very valuable scientific and practical results in the quantitative analysis of complex hydrocarbon mixtures [15]. In the USSR, N. D. Zelinskii was the pioneer in the domain of studying organic reactions at ultrahigh pressures, i.e., at pressures above 1000 atm. Together with L. F. Vereshchagin he studied the transformations of organic compounds in a broad span of pressures ranging from 2000 to 30,000 atm [16].

His numerous students have followed and always will follow the example of N. D. Zelinskii. Bowing with a sense of deepest respect before the bright memory of the head of the largest Soviet school of organic chemists — Academician Nikolai Dmitrievich Zelinskii — they together with the chemical community will give all of their strength and knowledge to the matter of the exaltation and well-being of our dear Country.

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PHYSICOCHEMICAL STUDY OF SYSTEMS CONTAINING DIPHENYLAMINE. II.

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Continuing our study of the reaction of diphenylamine with analogs of acetic acid, we measured the density, viscosity, electrical conductivity and fusibility of systems formed by diphenylamine with monochloro-, monobromo-, moniodo-, di- and trichloroacetic acids.

The method of operation was described earlier [1]. The monochloroacetic acid used in the study melted at 62.5°, monobromoacetic acid melted at 49.5°, and trichloroacetic acid melted at 58°. The dichloroacetic and monoiodoacetic acids were synthesized by us [2, 3]. After appropriate purification they melted at 8.8 and 82.5° respectively.

System diphenylamine-monochloroacetic acid. This system was studied by Tsvetkova and Dionis'ev [4], who established the absence of reaction in the solid phase. The results of our measurements are given in Tables 1 and 2. The system does not exhibit shrinkage; the maximum deviation of the density from additivity is found at 20 mole % diphenylamine. The viscosity isotherms pass through both a maximum and a minimum, which on raising the temperature are shifted toward the monochloroacetic acid side. The electrical conductivity isotherms have the shape shown in Fig. 1.

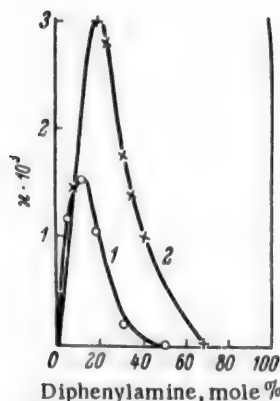


Fig. 1. Electrical conductivity of systems. 1) Diphenylamine-monochloroacetic acid (70°); 2) diphenylamine-trichloroacetic acid (100°).

Based on the thermal analysis results (Fig. 2), obtained by us using an N. S. Kurnakov pyrometer, the system has one eutectic at 34.8° and 56 mole % diphenylamine. These values differ somewhat from those given in the literature (37.5° and 50 mole % [4]).

The system diphenylamine-dichloroacetic acid was not studied before. The results of our measurements are given in Tables 2 and 3. The maximum shrinkage in this system (2.7%) is found at 25 mole % diphenylamine. The maximum on the viscosity isotherms is found at 25 mole % diphenylamine, and on the electrical conductivity isotherms at 18 mole % diphenylamine. A thermal analysis of the system was not made, since the mixtures on cooling did not crystallize, and instead changed to a glassy mass.

The system diphenylamine-trichloroacetic acid was studied by Tsvetkova and Dionis'ev [4]. The results of our measurements are given in Tables 2 and 4. The maximum shrinkage (4.8%) is found at 30 mole % diphenylamine. The density values for the middle portion of the diagram are found by interpolation due to decomposition of the trichloroacetic acid. On the viscosity isotherms the maximum is found at 31 mole % diphenylamine (Fig. 3), and on the electrical conductivity isotherms is found at 20 mole %. The dystectic maximum (m.p. 112.5°) is found at 50 mole % diphenylamine. After recrystallization, the equimolecular compound melted at 118.5°. When treated with alkalis and hot water the substance decomposes into diphenylamine and trichloroacetic acid, which can be titrated quantitatively.

From the mixtures containing 60-70 mole % diphenylamine, heated in small flasks at 120-130°, we isolated a new reddish-brown substance with a metallic luster (under the microscope it can be seen that these are droplets of

TABLE 1

System Diphenylamine-Monochloroacetic Acid

Mole % diphenyl- amine	Density			Viscosity (centipoises)			Mole % diphenyl- amine	M. p.	
	60°	70°	80°	60°	70°	80°		mixture	eutectic
0.00	1.3757	1.3625	1.3497	2.563	2.086	1.774	0.00	62.5°	—
9.99	1.3182	1.3061	1.2900	3.694	2.735	2.109	8.14	59.2	—
11.56	1.3097	1.2958	1.2851	4.125	3.049	2.370	15.55	54.7	—
15.55	1.2871	1.2759	1.2630	4.252	3.125	2.402	20.33	49.7	34.7°
20.33	1.2620	1.2468	1.2368	4.361	3.179	2.458	21.31	49.3	35.2
21.31	1.2565	1.2428	1.2323	4.292	3.136	2.422	25.90	46.5	35.7
25.90	1.2366	1.2249	1.2134	4.214	3.078	2.404	31.08	43.7	34.7
31.08	1.2131	1.2024	1.1908	4.109	3.041	2.372	40.00	41.9	34.7
38.19	1.1869	1.1750	1.1656	3.996	2.964	2.345	50.00	38.5	34.9
48.59	1.1559	1.1457	1.1352	3.860	2.907	2.296	60.00	39.0	34.9
62.17	1.1200	1.1107	1.1024	3.851	2.927	2.383	62.17	40.5	34.8
69.98	1.1027	1.0935	1.0861	3.925	3.001	2.394	69.98	45.1	34.8
80.74	1.0822	1.0728	1.0644	4.060	3.065	2.448	80.74	48.0	34.9
100.00	1.0555	1.0483	1.0403	4.375	3.293	2.579	100.00	53.5	—

TABLE 2

Electrical Conductivity of Binary Systems

Diphenyl - monochloro- acetic acid				Diphenylamine-dichloro- acetic acid				Diphenylamine-trichloro- acetic acid			
mole % diphenyl- amine	$\kappa \cdot 10^5 \text{ ohm}^{-1} \cdot \text{cm}^{-1}$			mole % diphenyl- amine	$\kappa \cdot 10^5 \text{ ohm}^{-1} \cdot \text{cm}^{-1}$			mole % diphenyl- amine	$\kappa \cdot 10^5 \text{ ohm}^{-1} \cdot \text{cm}^{-1}$		
	60°	70°	80°		50°	70°	80°		100°	110°	120°
0.00	1.14	1.44	1.75	—	—	—	—	0.00	0.012	0.016	0.021
5.58	111	119	125	4.22	0.73	1.15	1.38	7.78	0.015	0.018	0.019
11.17	146	153	153	14.60	1.50	2.62	3.32	18.63	306	367	438
18.47	102	108	102	22.43	1.28	2.52	3.24	22.82	281	324	434
27.18	44.3	42.8	39.8	25.03	1.00	1.88	2.65	29.71	175	242	267
30.59	22.0	20.1	17.7	35.12	0.82	1.77	2.12	34.66	136	182	210
51.42	1.57	1.34	1.24	49.62	0.40	0.71	0.85	41.45	107	141	187
61.80	0.26	0.25	0.23	74.95	0.017	0.02	0.02	50.14	68.8	90.4	120
70.77	0.099	0.096	0.094	—	—	—	—	68.35	1.02	21.0	—

tar). An alcohol solution of the substance has a blue color, changing under the influence of alkali first to a reddish-brown, and then to a yellow color. All of the described properties of the obtained substance, including the melting point (180-200°, with decompn.), are fully comparable to properties of diphenylamine "blue", which may be obtained from diphenylamine and oxalic acid [5].

Elemental analysis of the substance gave the following results.

Found %: C 79.8; H 5.53; N 7.59. $\text{C}_{37}\text{H}_{30}\text{N}_3\text{Cl}$. Calculated %: C 80.5; H 5.4; N 7.6.

A spectrophotometric study of the dye obtained by us in anhydrous alcohol revealed that the absorption maximum is found at 590-595 m μ . This is in good agreement with the literature data for diphenylamine "blue", namely 592.5 m μ [6].

System diphenylamine-monobromoacetic acid. This system was studied by Pushin [7] by the fusion method, who established the absence of reaction in the solid phase. It proved that the system could be studied only in the diphenylamine concentration limits ranging from 0 to 13.6 and from 78.8 to 100 mole %. At other concentrations the viscosity, and especially the electrical conductivity, increased noticeably with time. As far as can be judged

from the obtained data, the general shape of the viscosity isotherms should resemble their course in the system containing monochloroacetic acid.

After heating the mixtures containing from 14 to 79 mole % diphenylamine for 6-8 hr at 80° with subsequent cooling a crystalline substance separates, which after recrystallization from acetic acid melts at 225-230°. When treated with hot water the substance decomposes with ease into diphenylamine and hydrogen bromide, which can be titrated quantitatively. Elemental analysis gave the following results.

Found %: C 57.71; H 4.82; N 32.1. $C_{12}H_{11}N \cdot HBr$. Calculated %: C 57.6; H 4.84; N 31.95.

TABLE 3

System Diphenylamine-Dichloroacetic Acid

Mole % diphenyl- amine	Density			Viscosity (centipoises)		
	50°	70°	80°	50°	70°	80°
0.00	1.5152	1.4905	1.4785	3.225	2.069	1.710
4.22	1.4965	1.4713	1.4586	5.840	3.601	2.956
14.60	1.4384	1.4160	1.4050	20.060	8.938	6.876
22.43	1.3921	1.3681	1.3560	31.253	12.438	8.543
25.03	1.3767	1.3540	1.3431	33.337	12.752	8.711
26.92	1.3630	1.3410	1.3302	33.060	12.454	8.442
35.12	1.3173	1.2964	1.2862	29.765	11.038	7.494
49.62	1.2445	1.2240	1.2140	18.596	7.531	5.339
74.95	1.1390	1.1185	1.1112	8.610	4.193	3.220
100.00	1.0635	1.0486	1.0403	6.105	3.295	2.578

TABLE 4

System Diphenylamine-Trichloroacetic Acid

Mole % diphenyl- amine	Density			Viscosity (centipoises)			Mole % diphenyl- amine	M. p.	
	100°	110°	120°	100°	110°	120°		mixture	eutectic
0.00	1.5495	1.5352	1.5191	1.891	1.561	1.353	10.0	46.7°	28.0°
7.78	1.5105	1.4986	1.4857	3.796	2.952	2.424	15.0	31.2	28.0
18.63	1.4573	1.4469	1.4370	10.510	7.236	5.704	25.0	86.8	—
22.82	1.4440	1.4282	1.4170	13.770	10.235	7.378	30.0	101.9	—
29.71	1.4080	1.3972	1.3853	17.627	11.638	8.466	40.0	109.4	—
34.66	1.375 *	1.365 *	1.354 *	15.700	10.770	7.704	45.0	112.0	—
41.45	1.335 *	1.324 *	1.314 *	11.820	7.982	5.992	50.0	112.5	—
50.14	1.280 *	1.270 *	1.260 *	—	5.126	4.167	55.0	111.0	—
68.35	1.175 *	1.165 *	1.155 *	3.484	2.809	—	60.0	108.2	—
79.18	1.1191	1.1100	—	—	—	—	65.0	106.8	—
89.02	1.0673	1.0590	1.0510	—	—	—	75.0	101.0	—
100.00	1.0253	1.0166	1.0086	1.629	1.347	1.128	80.0	98.5	—
							90.0	77.5	52.5

*Values obtained by interpolation.

The system diphenylamine-monoiodoacetic acid was not studied before. We were able to study it only by the fusion method (Table 5). The components do not react in the solid phase (Fig. 3). The eutectic contains 65 mole % diphenylamine and melts at 40.8°.

In our work we used freshly prepared mixtures, which turned a dark green color very rapidly. From an equimolecular mixture of the components, heated on the water bath in sealed ampoules for 3 hr, we isolated a substance that in its properties resembled diphenylamine "blue". The substance chars at 180-190° without melting. However,

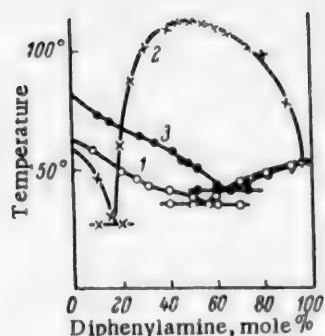


Fig. 2. Fusion curves. 1) System diphenylamine-monochloroacetic acid; 2) system diphenylamine-trichloroacetic acid; 3) system diphenylamine-monoiodoacetic acid.

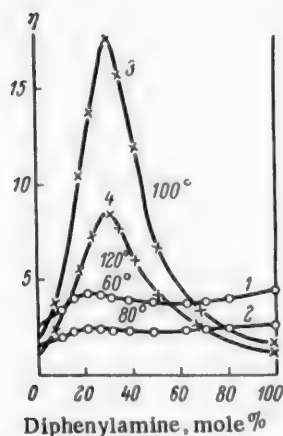


Fig. 3. Viscosity isotherms. 1 and 2) System diphenylamine-monochloroacetic acid; 3 and 4) system diphenylamine-trichloroacetic acid.

elemental analysis did not give completely desirable results, the reason for which was probably the presence of reaction products of different composition than the dye, and in particular the salt $C_{12}H_{11}N \cdot HI$. We obtained the latter by reacting HI with a benzene solution of diphenylamine. It had m.p. 196-198°. The absorption spectrum of the substance in anhydrous alcohol shows a maximum at 590-595 mμ.

From the literature it is known that the viscosity minimum is always shifted toward the component with the greatest temperature coefficient [8]. In the diphenylamine-monochloroacetic acid system the minimum is located between the viscosity of diphenylamine and the maximum viscosity. In this system the viscosity minimum is shifted toward the maximum, i.e., in the direction where the temperature coefficient is greater (at the maximum point the temperature coefficient of the viscosity is greater than in the case of diphenylamine).

In all of the systems of diphenylamine with halo-substituted acetic acids the maximum on the viscosity diagrams is shifted slightly toward the acid when the temperature is raised. If in the system with trichloroacetic acid this corresponds to a shift toward the more viscous component, then in the systems with dichloroacetic and monochloroacetic acids this shift is toward the less viscous component. A shift of the viscosity maximum along the composition axis is also determined by the ratio of the temperature coefficients.

In the diphenylamine-trichloroacetic acid system the viscosity maximum is very close to a 1:2 ratio of the components, from which it follows that the compound with composition $(C_6H_5)_2NH \cdot 2CCl_3COOH$ is formed in the liquid phase.

In the systems of diphenylamine with halo-substituted acetic acids the viscosity maximum is shifted toward the acid, and for dichloroacetic acid it is found at a 1:3 ratio, and for monochloroacetic acid at a 1:4 ratio. However, it should be remembered that the character of the reaction of these acids with diphenylamine is the same as in the case of trichloroacetic acid, but since the strength of the acid in this series decreases, then less stable compounds are formed, and the weaker the acid the greater the excess needed for the reaction to find reflection on the viscosity isotherms. In a system with such a weak acid as acetic acid the maximum on the viscosity isotherms is absent.

In their properties the systems of diphenylamine with monochloroacetic, monobromoacetic and monoiodoacetic acids exhibit a well-defined difference, which cannot be explained only by the differences in the dissociation constants of the acids: In the first system the properties remain constant with time; in the diphenylamine-monobromoacetic acid system, together with complex-formation, the acid decomposes and the compound $C_{12}H_{11}N \cdot HBr$ is obtained; while in the mixtures with monoiodoacetic acid the decomposition is accompanied by the formation of triphenylparafuchsin hydriodide. In the given case the difference in the behavior of the systems is determined by the influence exerted by the nature of the halogen on the character of the processes taking place.

It is known that chloro-substituted acetic acids in the presence of aromatic amines, even at low temperature, are decomposed into $CHCl_3$, CO_2 , and in part to HCl [9]. It is also known that amines are easily capable of entering into condensation reactions, forming di- and triphenylmethane derivatives [10]. In the presence of diphenylamine at elevated temperature a decomposition of the trichloroacetic acid takes place, accompanied by the evolution of CO_2 , HCl and $CHCl_3$. The carbon dioxide molecules can probably serve as condensation centers, leading (under the experimental conditions) to the formation of the parafuchsin derivative, having the structure of triphenylparafuchsin hydrochloride, known in the dye industry as "aniline blue". The condensation reaction, leading to the formation of

TABLE 5

System Diphenylamine - Monoiodoacetic Acid

Mole % diphenyl- amine	M. p.		Mole % diphenyl- amine	M.p.	
	mixture	eutectic		mixture	eutectic
0.00	82.5°	—	42.08	56.7°	39.5°
2.88	78.9	—	44.75	53.3	39.3
5.94	76.4	—	48.05	52.5	40.0
8.39	74.6	—	51.95	49.8	40.4
10.42	73.0	—	55.61	46.9	40.6
13.25	71.0	—	60.55	43.3	40.7
15.51	70.1	—	66.06	40.8	—
18.92	69.0	—	73.00	44.3	40.5
24.14	66.0	—	82.46	47.7	40.4
27.38	64.0	40.0°	91.97	51.7	—
34.07	61.5	40.8	100.00	53.5	—

triphenylparafuchsin, occurs in all of the systems, but the rate and completeness of its progress are different, in which connection the most favorable conditions exist in the systems containing the monoiodo- and trichloroacetic acids.

SUMMARY

1. The binary systems of diphenylamine with monochloroacetic, trichloroacetic and monoiodoacetic acids were studied by the fusion method.
2. The formation of a crystalline compound with composition $(C_6H_5)_2NH \cdot CCl_3COOH$ was established in the diphenylamine-trichloroacetic acid system.
3. A crystalline compound of composition $(C_6H_5)_2NH \cdot HBr$ separates in the diphenylamine-monobromoacetic acid system, obtained when the mixture of the components is heated above 80° due to decomposition of the monobromoacetic acid.
4. The binary systems of diphenylamine with monochloroacetic, dichloroacetic, trichloroacetic and monobromoacetic acids were studied at different temperatures on the basis of the density, viscosity and electrical conductivity. It was established that reaction takes place in the liquid phase of these four systems, being expressed as maxima on the viscosity and electrical conductivity isotherms, not coinciding exactly with a rational ratio of the components.
5. Triphenylparafuchsin hydrochloride was obtained as the condensation product of diphenylamine with trichloroacetic acid, while triphenylparafuchsin hydroiodide was obtained when condensation was with monoiodoacetic acid.

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ALKYL CARBONATE SALTS

V. METHYL CARBONATE SALTS OF BIVALENT METALS

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In previous communications data were presented on alkyl carbonate salts containing the univalent metals: sodium [1], potassium [2], and lithium and rubidium [3].

Literature data on the preparation of the magnesium methyl carbonate and barium methyl carbonate salts are given in Communication I [1].

Buzagh [4] mentioned that in his preparation of colloidal solutions of the carbonate salts of the alkaline-earth metals, in particular of CaCO_3 , by the Neuberg method [5] of passing carbon dioxide into a methanol suspension of calcium oxide, he also observed the formation of the calcium dimethyl carbonate salt $\text{CH}_3\text{OCOOCaOCOOCH}_3$. The author indicated that an analogy existed in the behavior of strontium oxide and calcium oxide but failed to give the details.

EXPERIMENTAL

The methyl carbonate salts of the bivalent metals were prepared from the methylates of the corresponding metals, obtained in turn from the metals and methanol. The metals used to prepare the salts, based on the analysis data, contained, in percent: Mg 99.60; Ca 99.32; Sr 98.48; Ba 98.93. Magnesium methylate was obtained as a thick slurry when 400 ml of methanol was heated under reflux with 4 g of magnesium turnings previously washed with ether. Calcium methylate was obtained by the addition of 3.6 g of calcium to 500 ml of methanol at room temperature. The turbid layer was decanted, and the precipitate was treated with 250 ml of methanol. The thus obtained suspension was used to prepare the salt. Strontium methylate, the same as barium methylate, was obtained by the gradual addition of 12 g of the metal to 900 ml of methanol cooled to -18° . The solution was filtered from a small amount of deposit using a Schott filter under a slight vacuum.

The magnesium methyl carbonate salt $(\text{CH}_3\text{OCOO})_2\text{Mg}$ was obtained by the passage of carbon dioxide into a thick slurry of magnesium methylate at $25-30^\circ$ until a clear solution of the magnesium methyl carbonate salt was formed. The methanol was removed by distillation under a slight vacuum. Traces of methanol were removed from the pulverized salt in a vacuum desiccator, also under a slight vacuum. $(\text{CH}_3\text{OCOO})_2\text{Mg}$ forms a clear viscous mass in chloroform or ethanol. It dissolves in water to yield a turbid solution (basic magnesium salts). d_4^{20} 1.318.

Found %: Mg 13.85, 13.87; C 27.66, 27.78; H 3.78, 3.68. $\text{C}_4\text{H}_6\text{O}_6\text{Mg}$. Calculated %: Mg 13.94; C 27.54; H 3.47.

The calcium methyl carbonate salt $(\text{CH}_3\text{OCOO})_2\text{Ca}$ was obtained by the passage of carbon dioxide into a methanol suspension of calcium methylate at 20° . At the start, as the CO_2 was passed in, the friable calcium methylate precipitate dissolved completely, and then the calcium methyl carbonate salt began to form as a crystalline precipitate. In some experiments a peculiar "superprecipitation" was observed — the friable methylate precipitate was converted to the crystalline salt precipitate. After filtering the precipitate on a Schott filter, with protection from atmospheric moisture, the traces of methanol were removed in vacuo. d_4^{20} 1.629.

Found %: Ca 21.72, 21.74; C 24.94, 24.61; H 3.29, 3.24. $\text{C}_4\text{H}_6\text{O}_6\text{Ca}$. Calculated %: Ca 21.08; C 25.26; H 3.18.

The strontium methyl carbonate ($\text{CH}_3\text{OCOO})_2\text{Sr}$ (d^{20}_4 2.214) and barium methyl carbonate ($\text{CH}_3\text{OCOO})_2\text{Ba}$ (d^{20}_4 2.383) salts were obtained by the passage of carbon dioxide into methanol solutions of strontium (at 20°) and barium (at -18°) methylates. After filtering the salts, the traces of methanol were removed from the strontium salt in the same manner as from the calcium salt, and in the case of the barium salt by washing with ether.

Found %: Sr 36.76, 36.87; C 20.34, 20.36; H 2.76, 2.69. $\text{C}_4\text{H}_6\text{O}_6\text{Sr}$. Calculated %: Sr 36.86; C 20.21; H 2.54.

Found %: Ba 47.84, 47.88; C 16.18, 16.31; H 2.10, 2.11. $\text{C}_4\text{H}_6\text{O}_6\text{Ba}$. Calculated %: Ba 47.83; C 16.71; H 2.10.

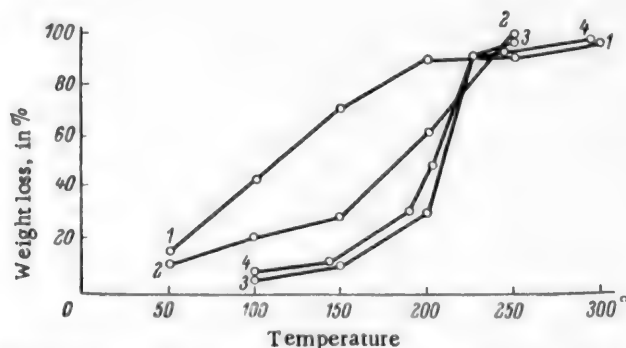
The barium methyl carbonate salt melts at $190-194^\circ$ (decompn.).

The methyl carbonate salts containing bivalent metals were analyzed for the amount of metal volumetrically [6].

Thermal Decomposition of Methyl Carbonate Salts Containing Bivalent Metals

The curves showing the weight loss incurred in the thermal decomposition of the methyl carbonate salts of bivalent metals as a function of the temperature are given in the graph.

The gaseous products evolved as the result of the thermal decomposition of the magnesium methyl carbonate salt at $260-272^\circ$, of the strontium methyl carbonate salt at $200-230^\circ$, and of the barium methyl carbonate salt at $250-270^\circ$ contain only carbon dioxide; neither carbon monoxide nor ethylene was evolved.



Dependence of the loss in weight of methyl carbonate salts of bivalent metals on the temperature of heating.

The evaporating liquid was composed of methanol with traces of formaldehyde and dimethyl ether. The solid residues contained (in %): Mg 28.03; Sr 57.67; Ba 68.13. The weight losses from the ignitions (tarry substances) were (in %): for magnesium methyl carbonate salt 2.1, for strontium methyl carbonate 2.8, and for barium methyl carbonate 2.5. The solid residues remaining after the ignitions were the pure carbonates of the corresponding metals. Since neither carbon monoxide nor unsaturated hydrocarbons are evolved in the decomposition of the methyl carbonate salts of bivalent metals, which did occur in the decomposition of the alkyl carbonate salts of univalent metals [1-3], it is postulated that the decomposition of the former salts proceeds by a simpler mechanism than does the decomposition of the latter salts.

SUMMARY

1. The calcium methyl carbonate ($\text{CH}_3\text{OCOO})_2\text{Ca}$ and strontium methyl carbonate ($\text{CH}_3\text{OCOO})_2\text{Sr}$ salts were obtained in the crystalline state; we determined the densities of the methyl carbonate salts of magnesium, calcium, strontium and barium, and the melting point of the barium salt.

2. Thermally the least stable salt is magnesium methyl carbonate, and the most stable are strontium methyl carbonate and barium methyl carbonate.

3. The gaseous product from the thermal decomposition is carbon dioxide, the liquid product is methanol (with traces of formaldehyde and dimethyl ether), and the solid products are the carbonates of the corresponding metals with a small amount of tarry substances as impurity.

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SPECTROSCOPIC STUDY OF THIONE-THIOL TAUTOMERISM

I. INFRARED ABSORPTION SPECTRA OF THIOUREA, PHENYLTHIOUREA, ASYMMETRICAL DIPHENYLTHIOUREA AND SYMMETRICAL DIPHENYLTHIOUREA

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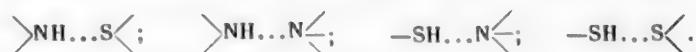
Among the various types of prototropic tautomeric transformations, the thione-thiol tautomerism is unfortunately the least studied, despite the fact that it possesses substantial theoretical and practical interest, especially since many sulfur-containing compounds find broad use in the rubber industry, medicine, photography, etc. Together with this, some of the published data on this subject [1-7] are contradictory and require additional study.

We employed the spectroscopic method to study the ability of thiourea and its three phenyl derivatives to undergo thione-thiol tautomeric transformation.

It is possible to postulate the existence of the following tautomeric forms of the thioureido group:



The tautomeric equilibrium usually exists in solution. However, the existence of different tautomeric forms also in the crystalline state is not excluded. Mention should also be made of the possibility of the thiono and thiol forms of the molecule reacting not only with the solvent molecules, but also with each to form associates through hydrogen bonding of the types:



The present communication is devoted to a study of the infrared absorption spectra of thiourea, phenylthiourea, and diphenylthiourea (asym. and sym.) both in the crystalline state and in carbon tetrachloride solution.*

The infrared absorption spectra in the 3500-500 cm^{-1} region were obtained using a modernized IKS-11 single-beam infrared spectrometer, with recording of the spectra on the ribbon chart of an ÉPP-09 electronic potentiometer. A Nernst stem and Silit resistor (globate) were used as the source of the infrared radiation. The proper filters were used to take care of the parasitic scattering of the radiation. The width of the slit in the investigated region of the spectrum was varied from 15 to 4 cm^{-1} . For a more accurate estimate of the intensity of absorption a supplemental study was made of the 1600-1400 cm^{-1} region using an IKS-2 double-beam spectrometer.

To obtain the spectra of the crystalline materials we used the following techniques to prepare the samples:

a) crystallization of the substance on the surface of a salt plate from a low-boiling solvent; b) suspension of the substance in Nujol; c) molding tablets of the investigated substance with KBr; d) sublimation of the substance on the mirror face of a special vacuum cell with a somewhat modified optical scheme of the illuminator [8]. In all cases the position and relative intensity of the spectral absorption bands could be reproduced quite accurately. The average values of the absorption band wave numbers, obtained by various techniques, are given below

(I) Thiourea: 3375, 3267, 3175, 2928, 2680, 1607, 1473, 1418, 1086, 730, 629 cm^{-1} .

(II) Phenylthiourea: 3420, 3285, 3190, 3015, 2980, 2930, 2675, 1606, 1580, 1520, 1468, 1310, 1292, 1270,

*The compounds were kindly supplied by I. I. Levkoev, for which the authors express their gratitude.

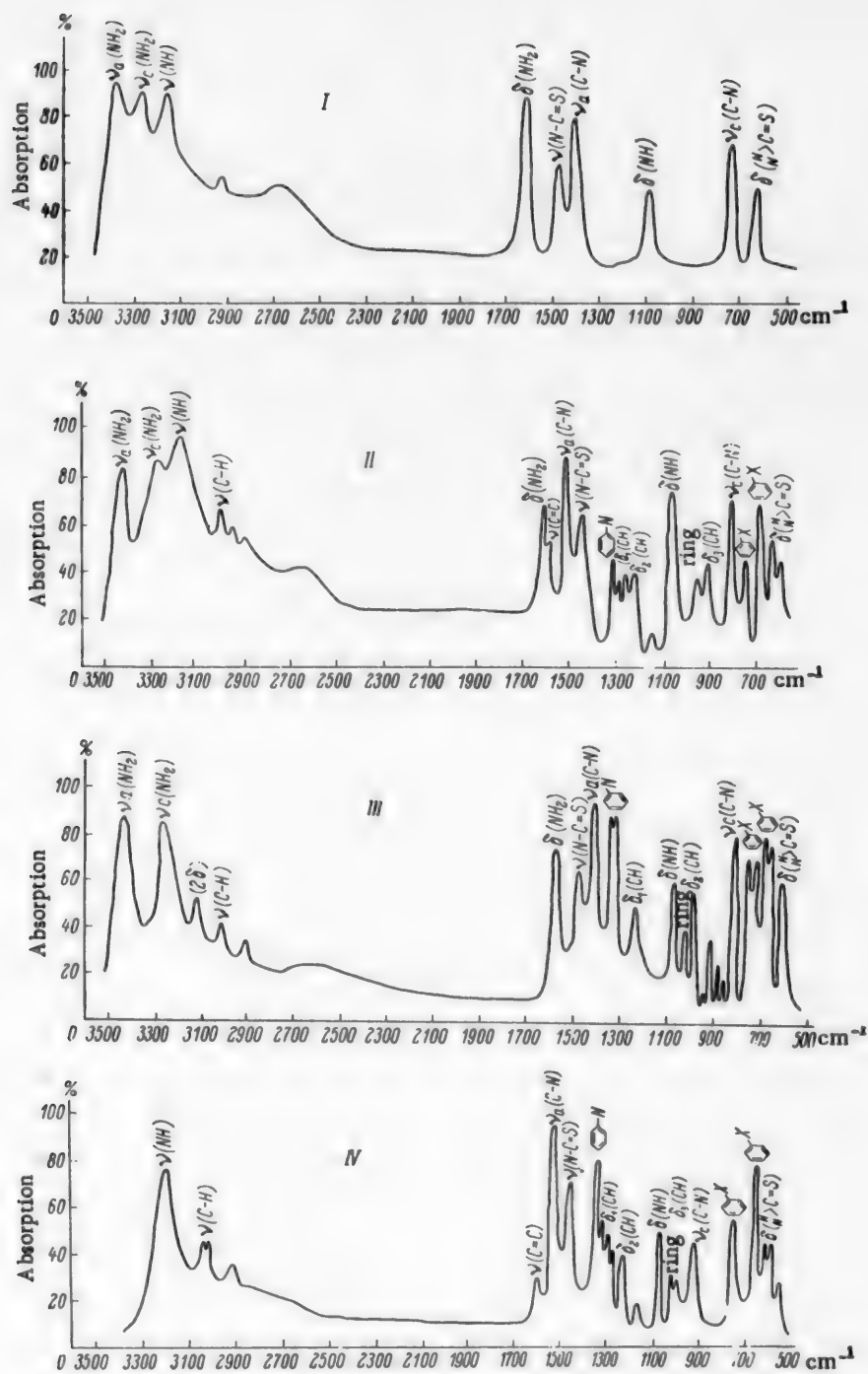


Fig. 1. Infrared absorption spectra of crystalline: thiourea (I); phenylthiourea (II); asym. diphenylthiourea (III); sym. diphenylthiourea (IV).

1230, 1156, 1060, 966, 918, 810, 750, 694, 610 cm^{-1} .

(III) Diphenylthiourea (asym.): 3448, 3280, 3150, 3035, 2928, 2630, 1585, 1485, 1432, 1350, 1334, 1256, 1073, 1020, 1002, 978, 934, 920, 910, 820, 768, 737, 704, 694, 628 cm^{-1} .

(IV) Diphenylthiourea (sym.): 3220, 3040, 3015, 2930, 1600, 1530, 1460, 1340, 1318, 1300, 1278, 1244, 1178, 1074, 1024, 1008, 936, 760, 669, 646, 630, 614 cm^{-1} .

The corresponding spectral curves are shown in Fig. 1. We used a cell with a thickness of 50 mm for recording the infrared spectra of very dilute solutions of the phenyl derivatives of thiourea in CCl_4 .

Discussion of Results

For the thiono form of thiourea and its phenyl derivatives the characteristic absorption bands are [9]: a) valence vibration bands of the primary and secondary amino groups $\nu(\text{NH})$ in the 3500-3100 cm^{-1} region; b) deformation vibration band of the NH_2 group $\delta(\text{NH}_2)$ in the 1650-1590 cm^{-1} region; c) valence vibration band of the $\text{C}=\text{S}$ bond $\nu(\text{C}=\text{S})$, characteristic in the presence of the nitrogen atom, i.e., the band of the thioureido grouping $-\text{NH}-\text{C}=\text{S}$, which is quite intense and lies in the 1500-1460 cm^{-1} interval; d) valence vibration band of the $\text{C}-\text{N}$ bond $\nu(\text{C}-\text{N})$.

For the thiol form the characteristic bands are [9]: a) valence vibration band of the $\text{S}-\text{H}$ group $\nu(\text{S}-\text{H})$, which is located in the 2600-2550 cm^{-1} interval and, based on existing data, has a low intensity; b) valence vibration band of the $\text{C}=\text{N}$ bond $\nu(\text{C}=\text{N})$ in the 1690-1640 cm^{-1} region; c) valence vibration band of the $\text{C}-\text{S}$ band $\nu(\text{C}-\text{S})$, located in the 700-600 cm^{-1} interval.

It is convenient to discuss the spectra obtained by us by comparing the separate regions of characteristic vibrations.

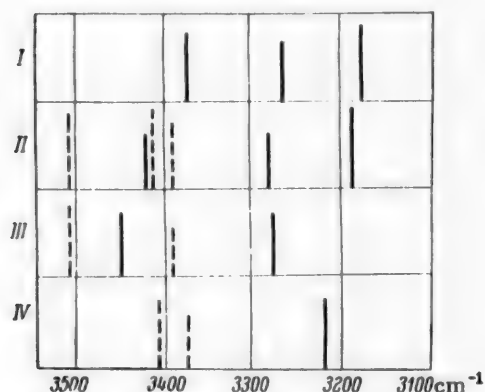


Fig. 2. Distribution scheme of the infrared valence vibration bands of the amino groups. Solid lines - absorption of crystalline compounds; dotted lines - absorption of dilute solutions of the same compounds in CCl_4 .

in the spectra of the crystalline compounds (II) and (III) suggest the presence of strong hydrogen bonding, the energy of which is affected by the difference in the structure of (II) and (III). In the spectra of crystalline (II) and (IV), containing one or two secondary amino groups, an intense band is found at 3190 and 3220 cm^{-1} respectively, which can be assigned to the valence vibrations of the bound $>\text{NH}$ group. In the spectra of dilute solutions of these compounds this band is also shifted toward shorter wavelengths and exhibits a frequency of 3415 and 3405 cm^{-1} respectively (Fig. 2). Difficulty is encountered in interpreting a second band found at 3375 cm^{-1} in the spectrum of solution (IV). It is possible that it is due to the interaction of the vibrations of two $>\text{NH}$ groups.

3500-2500 cm^{-1} region of valence vibrations. All of the investigated compounds exhibit a whole series of bands of variable intensity in this region, relating to the valence vibrations of $\text{N}-\text{H}$, $\text{C}-\text{H}$ (for the phenyl derivatives) and, it could be assumed, $\text{S}-\text{H}$. The most intense bands can quite definitely be assigned to the $\text{N}-\text{H}$ valence vibrations (Fig. 2). In the spectra of the crystalline compounds (I-III), having either two or one NH_2 group (Figs. 1 and 2), two bands with the frequencies (I) 3375 and 3267 cm^{-1} , (II) 3420 and 3285 cm^{-1} , and (III) 3448 and 3280 cm^{-1} can be reliably assigned respectively to the antisymmetrical, ν_a , and symmetrical, ν_s , valence vibrations of the NH_2 group.

In the spectra of dilute CCl_4 solutions of (II) and (III) (Fig. 2) these bands show considerable shift toward shorter wavelengths and exhibit in the case of these two compounds, each containing one NH_2 group, exactly coinciding frequency values: 3510 and 3390 cm^{-1} . On the one hand, this indicates that the different structure of these molecules (substituents on the second nitrogen atom) has very little effect on the vibration frequencies of the NH_2 group. On the other hand, the much lower value of the ν_a and ν_s frequencies and their difference

In the spectrum of crystalline thiourea the appearance of a third band with a frequency of 3175 cm^{-1} may also be due to the presence of two NH_2 groups. Unfortunately, thiourea is so insoluble in CCl_4 that we were unable to obtain a spectrum of its solution; however, in the crystalline state its molecules are undoubtedly linked by very strong hydrogen bonds, which is evidenced by the low values of the N-H vibration frequencies. For the phenyl derivatives of thiourea the bands of the C-H vibrations were also observed in the 3000 cm^{-1} region, which we will not discuss here. In addition, all of the compounds in the crystalline state exhibit in the discussed region weak absorption peaks, which may be either overtones or the principal valence vibration bands of primary or secondary amino groups. The diffuse absorption manifested in the spectra of crystalline (I-III) with a maximum in the $2700\text{--}2600\text{ cm}^{-1}$ interval could possibly be assigned to the S-H vibrations of the thiol forms. However, it is necessary to verify this postulation by data from other regions of the spectrum.


1650-500 cm^{-1} region. The deformation vibration bands of the amino groups, constant with respect to both position and intensity, are easily detected in the spectra of all of the investigated compounds. The frequencies of the internal (scissors) deformation vibrations of the primary amino group, $\delta(\text{NH}_2)$, for (I-III) are respectively equal to 1607, 1606, and 1586 cm^{-1} . The phenyl absorption band lying in this region is seen in the case of (II) as a separate peak with a frequency of 1580 cm^{-1} and hardly interferes in the case of (III), although it is superimposed on the $\delta(\text{NH}_2)$ band. In the spectrum of (IV), not containing a secondary amino group, it can be seen that the phenyl band at 1600 cm^{-1} is much less intense than the $\delta(\text{NH}_2)$ band in the spectra of (I-III).

All of the compounds also exhibit the deformation vibration bands of the amino group, $\delta(\text{NH})$, with the frequencies: (I) 1086, (II) 1060, (III) 1073, (IV) 1074 cm^{-1} .

As was to be expected, the frequency of the $>\text{C}=\text{S}$ valence vibrations is affected but slightly by the symmetry of the molecule and the nature of the substituents on the nitrogen atoms. In harmony with this, the band of the thioureido groupings shows little change in intensity and undergoes only slight shifts. The $\nu(\text{C}=\text{S})$ frequencies for (I-IV) are respectively equal to 1473, 1468, 1485 and 1460 cm^{-1} .

In contrast, the C-N valence vibrations should be strongly affected by substituents on the nitrogen atom. Actually, if for (I) the frequencies of the asymmetric, ν_a , and symmetric, ν_s , C-N valence vibrations are respectively equal to 1418 and 730 cm^{-1} , then for (II) the frequencies 1520 and 810 cm^{-1} relate to the C-N vibrations, for (III) 1432 and 820 cm^{-1} , and for (IV) 1530 and 936 cm^{-1} . As a result, the position of the C-N valence vibration bands changes greatly, which, however, cannot be said for their relative and absolute intensities.

All of the compounds exhibit the deformation vibration band $\delta\left(\begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{N} \end{array} \text{C}=\text{S}\right)$ in the 600 cm^{-1} region (Fig. 1).

In the spectra of the phenyl derivatives of thiourea the -N vibration band is observed in the 1300 cm^{-1} region, and also bands, corresponding to different vibration forms of the phenyl radicals, with frequencies at 1250 cm^{-1} and in the 1000, 950, 760-750 and $690\text{--}670\text{ cm}^{-1}$ regions.

In not a single spectrum of the investigated compounds were we able to detect bands that could be related to the C=N valence vibrations of the thiol form. The same can also be said for the C-S valence vibrations (at least in the case of thiourea); in the case of the phenyl derivatives a series of bands is found in the $700\text{--}600\text{ cm}^{-1}$ region; although we were unable to relate even one of these bands to the C-S vibrations, still it is impossible to say that superimposition of the bands does not exist here.

As a result, in the $1650\text{--}500\text{ cm}^{-1}$ region of the spectrum we do not find confirmation of the above-expressed through that substantial amounts of the thiol form exist in the molecules of thiourea and its phenyl derivatives. Still it is possible to assume, although this is not very probable, that the intensity of the absorption band of the S-H vibrations is great when compared with the band intensities of the C=N and C-S vibrations; for this reason, the first appears in the spectra of the investigated compounds, while the latter do not appear. Then it must be concluded that thiourea and its phenyl derivatives in the crystalline state exist primarily as the thiono form; if the thiol form is present, then its amount is insignificant.

SUMMARY

1. A study and interpretation were made of the infrared absorption spectra of thiourea, phenylthiourea, asym. diphenylthiourea and sym. diphenylthiourea in the crystalline state in the $3500\text{--}500\text{ cm}^{-1}$ region, and of the last three compounds in dilute CCl_4 solutions in the $3550\text{--}2800\text{ cm}^{-1}$ region.

2. It was shown that in the crystalline state the molecules of the investigated compounds are found to exist almost entirely as the thiono form. A comparison of the infrared spectra of these compounds with the spectra of their solutions in CCl_4 testifies to the presence of strong intermolecular hydrogen bonding in the crystalline state.

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ABSORPTION SPECTRA OF 3-OXO-2,3-DIHYDROTHIONAPHTHENE AND ITS DERIVATIVES. III.

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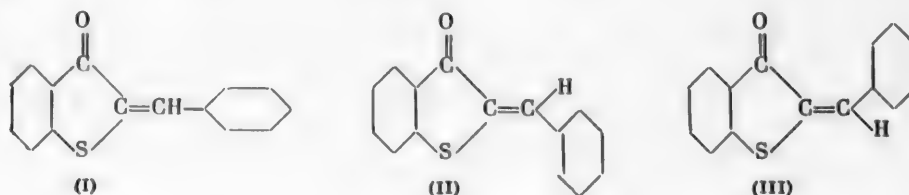
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 1, pp. 17-28,

January, 1961

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In connection with the study of the color of indigo and thioindigo from the point of view of the separation of the structure of conjugated systems [1, 2] of cochromophores [2] into polar chromophoric components [2] of the type AK and BK (A is an electron-donor chromophore, for example NH and S; B is an electron-acceptor chromophore, for example, CO and NO₂; and K is a conjugated system), we studied the spectra of systems with a simplified structure containing partial chromophoric components present in indigoids, namely the systems of 3-oxo-2,3-dihydrothionaphthene and 3-oxoindolenine.

It was shown previously [3] that the spectrum of 2-benzylidene-3-oxo-2,3-dihydrothionaphthene (I) in solutions changes during irradiation with light and that the reason for this is photochemical isomerization of (I). Two isomeric forms of 2-benzylidene-3-oxo-2,3-dihydrothionaphthene, which we designated by A and B, were isolated and characterized.



Form B had a more sterically hindered structure so that it had a lower melting point than form A, a higher solubility in organic solvents, and a lower molecular extinction. On the basis of an examination of approximate molecular structures of the stereoisomers which we constructed, the hypothesis was put forward that the more stable form A of compound (I) corresponds to the structure (II) and the form B, to the structure (III).

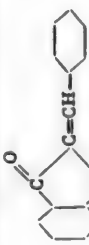
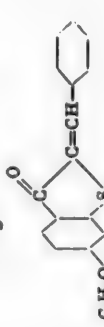

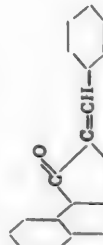

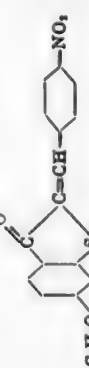
The present work was undertaken to determine whether the capacity for photochemical isomerization is a general property of analogs and substituted derivatives of (I). We synthesized 20 compounds (Table 1), 16 of which are described for the first time, and studied the phototropy of their solution. In all the cases investigated (Tables 1 and 2), the spectrum of a solution prepared in the dark changed appreciably on irradiation with visible light of appropriate wavelength. A considerable change in the spectrum was observed for solutions in alcohol and in benzene.* However, the presence in solution of two isomeric forms appeared much more clearly if n-hexane was used as the solvent. This is shown particularly well by a comparison of Figs. 1 and 2 for the case of (2-p-dimethylaminobenzylidene)-3-oxo-2,3-dihydrothionaphthene (No. 13, Table 1).** When a solution in n-hexane prepared in the dark (1, Fig. 2) was irradiated, on the absorption curve of compound No. 13 there arose a new, sharp maximum at 492.5 mμ, while at the same time the intensities of the sharp maxima at 434 and 462 mμ observed previously (2, Fig. 2) decreased, and this clearly indicates the partial conversion of form A of compound No. 13, which was initially present

*Analogous but considerably smaller changes in the spectrum of a solution of the dye Genacryl yellow in chloroform were observed by Wyman [4] and treated by him as manifestations of photochemical cis-trans isomerism.

**The numbers of all the dihydrothionaphthene compounds correspond to the numbers in Table 1.

TABLE 1

Substituted 2-Benzylidene-3-oxo-2,3-dihydrothionaphthenes and Their Furfurylidene Analogs

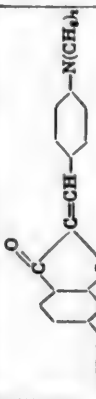


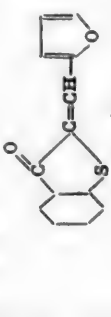
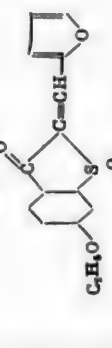
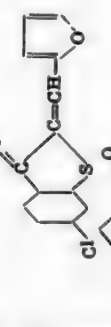
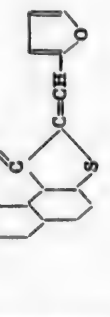
Sample No.	Formulas of compounds	Solvent*	Melting point	Empirical formula	% S			Content of other elements	
					found	calculated		found (%)	calculated (%)
1		E	132—132.5°, 131.5° [K]						
2		H	151—151.5	$C_{17}H_{14}O_2S$	11.23, 11.52	11.36			
3		AA	159.5—160	$C_{15}H_8OClS$	11.71, 11.82	11.75		Cl 12.98, 12.97	Cl 13.01
4		AA	163.5—164, 159 [15]	$C_{15}H_{12}OS$	10.92, 11.21	11.11			
5		CB	234—234.5, 231 [15]	$C_{15}H_8O_3NS$	11.36, 11.30	11.31		N 4.99, 5.15	N 4.95
6		CB	270.5—271	$C_{17}H_{12}O_4NS$	9.77, 9.86	9.80		N 4.22, 4.44	N 4.27

*Recrystallization solvents: ethanol (E), dilute aqueous methanol (M), n-hexane (H), acetic acid (AA), benzene (B), and chlorobenzene (CB).

TABLE 1 (continued)

Sample No.	Formulas of compounds	Solvent	Melting point	Empirical formula	% S		Content of other elements	
					found	calculated	found (%)	calculated (%)
7		CB	243—243.5°	$C_{15}H_8O_3NClS$			Cl 11.19, N 4.38	Cl 11.18, N 4.32
8		CB	290—290.5, 287 [15]	$C_{19}H_{11}O_3NS$			N 4.09, 4.12	N 4.20
9		M	158.5, 159.5	$C_{18}H_{13}O_3S$	11.69, 11.48	11.95		
10		B	151—152	$C_{18}H_{16}O_3S$	10.0, 10.26	10.26		
11		B	209.5—210	$C_{18}H_{11}O_2ClS$	10.32, 10.34	10.6	Cl 11.65, N 11.59	Cl 11.75
12		B	189.2—190	$C_{20}H_{14}O_3S$			C 75.61, H 4.43	C 75.3, H 4.4
13		B	172.5—173.5	$C_{17}H_{15}ONS$	11.22, 11.47	11.40	N 5.04, 5.21	N 4.98

TABLE 1 (continued)

Sample No.	Formulas of compounds	Solvent	Melting point	Empirical formula	% S		Content of other elements	
					found	calculated	found (%)	calculated (%)
14		E	174—174.5°	$C_{19}H_{19}O_2NS$	9.84, 9.97	9.85	N 4.32, 4.33	N 4.31
15		B	206.5—207	$C_{17}H_{14}ONClS$	9.95, 10.09	10.15	N 4.54, 4.65	N 4.45
16		CB	217.5—218.5	$C_{21}H_{17}ONS$			N 4.23, 4.21	N 4.22
17		H	133—133.5	$C_{13}H_8O_2S$			C 68.54, H 3.42	C 68.4, H 3.5
18		M	160—160.7	$C_{16}H_{13}O_3S$	11.59, 11.54	11.78		
19		B	191—192	$C_{13}H_7OClS$	12.06, 12.29	12.20	Cl 13.59, 13.69	Cl 13.5
20		B	176.5—177.5	$C_{17}H_{10}O_2S$	11.36, 11.62	11.5		

in solution, into the other form B.* In a benzene solution of compound No. 13, the photochemical formation of form B from form A was observed less clearly as irradiation of the solution prepared in the dark (1, Fig. 1) produced only an inflection (in the region of about 508 m μ) and not a maximum on the absorption curve (2, Fig. 1).

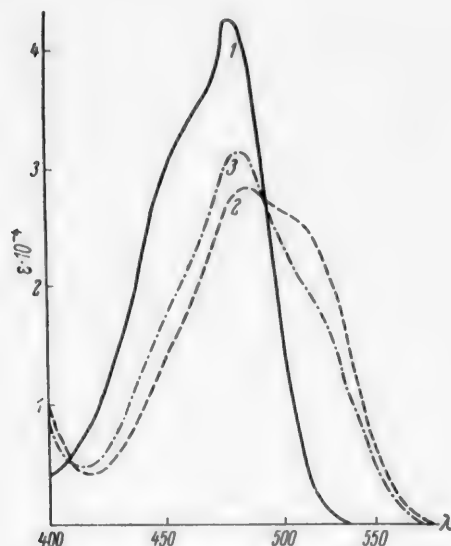


Fig. 1. Spectrum of benzene solution of compound No. 13. 1) After preparation in the dark, 2) after irradiation of previous solution (1) for 30 min with blue light on a FÉK-M photo-colorimeter, 3) after irradiation of previous solution (2) for 30 sec with direct sunlight.

The characteristics of the photoisomerization we studied were shown most clearly by an n-hexane solution of compound No. 13 (Fig. 2). The absorption curve of a solution prepared in the dark (1, Fig. 2) was the spectrum of the pure form A, as the ordinate of curve 1 in the region of the absorption maximum of form B (at 492 m μ) equaled zero. By using the calculation method proposed by Wyman and Brode [5] and assuming that the absorption intensity of form B equals zero at 490 m μ , it was possible to find the approximate absorption spectrum of form B (curve 3, Fig. 2) from curves 1 and 2 (Fig. 2).

The absorption curve of form A (1, Fig. 2) has a higher intensity at the main maximum and a clearly expressed subsidiary maximum. The absorption curve of form B (3, Fig. 2) obtained by calculation has a lower intensity at the maximum and does not have a second maximum. It is interesting to note that the absorption curve obtained experimentally for form B of unsubstituted 2-benzylidene-3-oxo-2,3-dihydrothionaphene has the same characteristics [3].

As the change in the spectrum of the solution under the action of light could have been produced by photochemical decomposition of the solute, it was necessary to establish the reversibility of the changes in the spectrum. The reversibility of the phototropic process could be observed in all cases when there was a light filter which transmitted wavelengths absorbed by form B and absorbed wavelengths absorbed by form A. For example, a solution of compound No. 13 prepared in the dark (1, Fig. 2) contained only form A. On irradiation with blue light, some of the

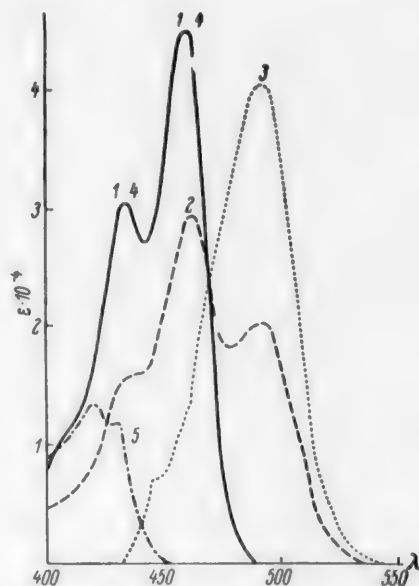


Fig. 2. Spectrum of n-hexane solution of compound No. 13. 1) After preparation in the dark, 2) after irradiation of previous solution (1) through a blue filter on a FÉK-M photo-colorimeter, 3) calculated curve for form B, 4) spectrum after irradiation of solution (2) with light from an electric lamp through a ZhS-18 light filter for 30 min, 5) spectrum of compound No. 1 in n-hexane.

*The terms "cis" and "trans" are not completely definite in the case of the unsymmetrical compounds we studied. In using them, it would be necessary to indicate in each case the substituents at the ethylene bond whose relative position was considered. For this reason and also because the steric structure of the stereoisomers studied has not yet been demonstrated strictly we use letters for indicating the stereoisomeric forms of (I) and analogous compounds. Form A is the form whose long-wave maximum is at the shorter wavelength. The other form with the deeper color is denoted by B.

molecules of form A were converted into an excited state. Some of the excited molecules lost the excitation energy without changing their configuration and others were converted into form B.* Since blue light was also absorbed by form B, in their turn, the molecules of the latter could be excited and then converted to form A so that an equilibrium was established in the solution between forms A and B (2, Fig. 2). If this solution with equilibrium established was irradiated with yellow light, which could only be adsorbed by molecules of form B, then the isomerization reaction $A \rightarrow B$ ceased, as molecules of form A could not absorb quanta of the incident light. Meanwhile, the photoisomerization $B \rightarrow A$ continued. However small the quantum yield of the latter process, the whole of the solute was gradually converted into form A. This yielded a solution whose spectrum completely coincided with that of a solution prepared in the dark (4, Fig. 2, coinciding completely with curve 1). Thus, the complete reversibility of the phototropic process was demonstrated in the given case.

TABLE 2

Phototropic Properties of n-Hexane Solutions of 2-Benzylidene-3-oxo-2,3-dihydrothionaphthene and Its Analogs and Substituted Derivatives*

Sample No.	Solution of form A (prepared in the dark)				Radiation source	Irradiation time (in min)**	Irradiated solution***		Isosbestic point	
	λ_{\max}	$\epsilon \cdot 10^{-4}$	λ_{\max}	$\epsilon \cdot 10^{-4}$			λ_{\max}	λ	$\epsilon \cdot 10^{-4}$	
1	420	1.3	430	1.2	Sunlight	1	443	436	0.7	
2	406	1.0	~418	0.72	Sunlight	2	426	422	0.6	
3	418	1.5	427	1.2	Sunlight	5	441	432	0.7	
4	434	0.9	~452	0.8	Light from 109 W lamp	30	456	462	0.5	
5	433		443		Daylight	5	454	454		
6	420		~436		Light from 109 W lamp	16	436	441		
7	430		~440		Daylight	5	446	446		
8	450		~475		Light from 109 W lamp	3	462	484		
9	~420	1.85	435	2.52	Diffuse daylight	8	460	441	2.36	
10	~410	1.68	420	1.73	Sunlight	0.5	~444	426	1.07	
11	409	1.82	433	2.76	Diffuse daylight	5	458	440	1.35	
12	435	1.4	454	1.58	Sunlight	5	~478	466	0.94	
13	434	3.1	462	4.5	Blue light	30	492.5	470	2.2	
14	421	3.4	444.5	4.7	Blue light	10	474	453	2.7	
15	439	3.8	466.5	5.5	Blue light	30	497	475	5.0	
16	452	3.4	482	4.7	Blue light	30	506	423	1.4	
								490	2.5	
17	430	1.79	439	1.9	Sunlight	5	456	447	1.45	
18	417	1.59			Sunlight	5	437	427.5	1.33	
19	~427	1.82	435	1.98	Diffuse daylight	5	455	444	1.52	
20	448	1.3	~456	1.07	Diffuse daylight	10	472	403	0.32	
								467	0.4	

*The numbers of the compounds correspond to the numbers in Table 1. An absorption maximum determined approximately from a bend in the curve is denoted by ~.

**For compounds Nos. 1, 4-10, 19, and 20, the irradiation time was sufficient for equilibrium to be established in solution between forms A and B.

***Only new absorption maxima are given. The maxima of form A, which did not always disappear completely during irradiation (see for example Figs. 2 and 3), are not mentioned.

The phototropic changes of compound No. 15 could also be reversed completely by irradiation of the isomerized** compound in solution for 30 min through a Zhs-18 light filter. Partial reversibility of the phototropic process was observed with the following compounds: No. 4 (by irradiation through the green light filter of a FEK-M

*For more detail see [6].

**Under the conditions given in Table 2.

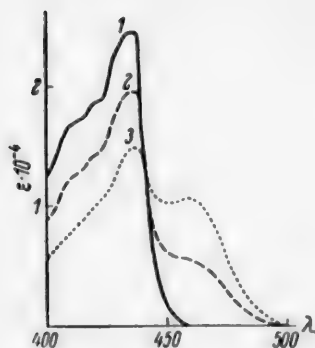


Fig. 3. Spectrum of n-hexane solution of compound No. 9. 1) After preparation in the dark, 2) after irradiation of previous solution (1) in sunlight for 30 sec, 3) after irradiation of previous solution (2) with sunlight for 5 min.

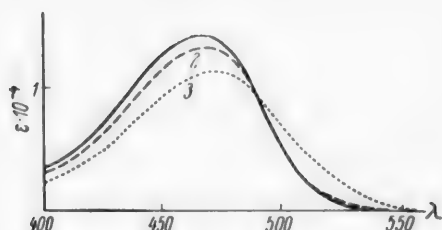


Fig. 5. Spectrum of compound No. 5 in benzene. 1) After preparation in the dark, 2) after irradiation of previous solution (1) with daylight for 30 sec, 3) after irradiation of previous solution (2) with daylight for 5 min.

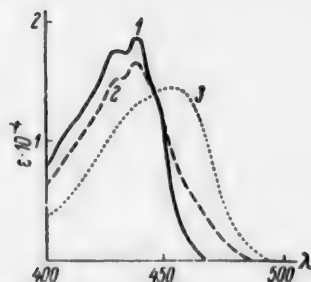


Fig. 4. Spectrum of compound No. 17 in n-hexane. 1) After preparation in the dark, 2) after irradiation of previous solution (1) with sunlight for 30 sec, 3) after further irradiation of previous solution (2) with sunlight for 5 min.

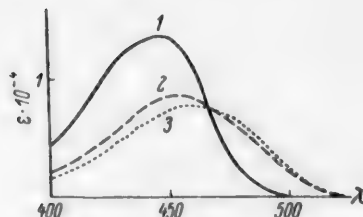
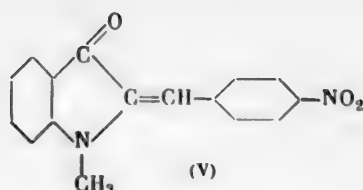
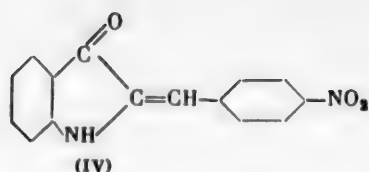


Fig. 6. Spectrum of 2-(p-nitrobenzylidene)-3-oxoindolenine in benzene. 1) After preparation in the dark, 2) after irradiation of previous solution (1) with sunlight for 30 sec, 3) after irradiation of previous solution (2) with sunlight for 5 min.

photocolorimeter), No. 10 (blue light filter of FÉK-M), No. 14 (ZhS-18 yellow light filter), and No. 16 (OS-11 orange light filter).

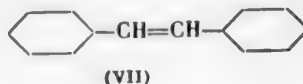
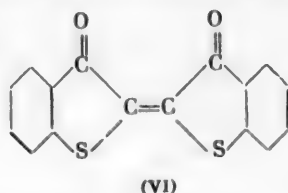
As the data in Table 2 show, photoisomerization in solution was undergone not only by derivatives of 2-benzylidene-3-oxo-2,3-dihydrothionaphthene with electrophilic groups (compounds Nos. 5-8) and electron-donor groups (compounds Nos. 9-16), but also by substituted 2-furfurylidene-3-oxo-2,3-dihydronaphthenes (compounds Nos. 17-20). Spectral curves of typical representatives of the types of compound listed are given in Figs. 3-5.

It is known that, in contrast to thioindigo, indigo is blue and *N,N'*-dimethylindigo is incapable of photoisomerization [7, 8]. Pummerer and his co-workers made a spectroscopic study of 2-benzylidene-3-oxo-indolenine, but did not observe isomerism with this compound [9]. In order to study the isomerization capacity of indolenine derivatives of this type, we synthesized 2-(p-nitrobenzylidene)-3-oxoindolenine (IV) and 2-(p-nitrobenzylidene)-3-oxo-*N*-methylindolenine (V).



As we expected, both of these substances were found to isomerize on irradiation with light of suitable wavelength (Figs. 6 and 7).

In conclusion, we would like to report certain preliminary conclusions on the effect of structural factors on the color and spectrum of compounds of type I. The molecule of (I) is unsymmetrical. The left-hand (thionaphthalene) part is half of the thioindigo molecule (VI) and the other (benzylidene) part is half of stilbene (VII). Substitution in different parts of the molecule of (I) should have a different effect on the color of the derivatives.



A comparison of compounds with the same right-hand part of the molecule (Nos. 1-4, and then Nos. 5-8, 9-12, 13-16, and 17-20 in Table 2) shows that as a rule, the color deepened in the order 6-ethoxythionaphthalene < 6-chlorothionaphthalene < thionaphthalene < 4,5-benzothionaphthalene, i.e., in the same order as with the corresponding symmetrical thioindigo dyes. The only exception was observed in the group of compounds with NMe_2 , Nos. 13-16, which have strong intramolecular polarization: Contrary to expectations, compound No. 15 was found to be deeper in color than compound No. 13.

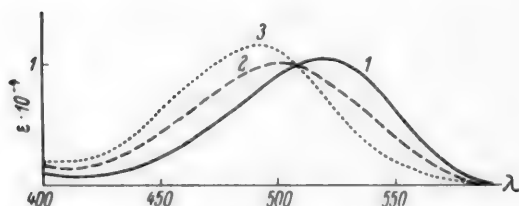


Fig. 7. Spectrum of 2-(p-nitrobenzylidene)-3-oxoindolenine in benzene. 1) After preparation in the dark, 2) after irradiation of previous solutions (1) with sunlight for 5 min, 3) after irradiation of previous solution (2) with a 109 W lamp through an OS-11 light filter for 30 min.

The extinctions of the compounds examined increased in the order: 4,5-benzothionaphthalene < 6-ethoxythionaphthalene < thionaphthalene < 6-chlorothionaphthalene. Deviations from this order were observed only in the series of compounds Nos. 13-16.

On examining compounds with the same left-hand part of the molecule, it is observed that the color deepens with an increase in the strength of the electron-donor substituent present in the benzylidene part of the molecule,

$\text{H} < \text{OCH}_3 < \text{N}(\text{CH}_3)_2$. At the same time the extinction increases. Thus, p-dimethylamino derivatives Nos. 13-16 have deeper and more intense colors than the corresponding p-methoxy derivatives Nos. 9-12, while the latter are deeper and more intense than compounds without substituents Nos. 1-4. The p-nitrobenzylidene derivatives Nos. 5-8 are deeper in color than the corresponding unsubstituted compounds Nos. 1-4. In order to compare the extinctions of these two groups of substances, we measured the absorption spectra of compounds Nos. 1-8 in benzene* (Table 3). The data in Table 3 show that the introduction of a nitro group hardly changed the extinction (Nos. 1, 5, 2, 6, 3, 7, 4, 8). Changes in the absorption spectra associated with the change from n-hexane to benzene solutions will not be considered here, as the solvatochromism of compounds Nos. 1-20 will be examined in detail in a later communication. The furfurylidene derivatives Nos. 17-20 have a deeper color than the corresponding benzylidene derivatives Nos. 1-4. Compound (V) has a deeper color than compound (IV) and the latter is deeper than substance No. 5, which is connected with the increase in the donor properties: $\text{N}(\text{CH}_3)_2 > \text{NH} > \text{S}$.

*Compounds Nos. 5-8 and also (IV) and (V) were sparingly soluble in hexane, and errors could arise in the determination of the extinction due to incomplete solution of the sample taken for preparing the solution. The substances mentioned were much more soluble in benzene and this danger was eliminated.

TABLE 3

Phototropic Properties of Benzene Solutions of Compounds Nos. 1-8 (irradiation with daylight for 5 min)*

Sample No.	Form A (solution prepared in the dark)				Irradiated solution	Isosbestic point	
	λ_{\max}	$\epsilon \cdot 10^{-4}$	λ_{\max}	$\epsilon \cdot 10^{-4}$	λ_{\max}	λ	$\epsilon \cdot 10^{-4}$
1	~422	1.2	434	1.33	444	446	0.74
2	409	1.02	~418	0.97	427	429	0.62
3	~420	1.3	432	1.44	441	442	0.81
4	441	0.90	~453	0.89	460	471	0.53
5	~432	1.23	448	1.36	458	466.5	0.76
6	—	—	428	1.23	443	454	0.60
7	~428	1.26	443	1.37	454	458	0.73
8	—	—	458	0.87	467	—	—

*The numbers correspond to the numbers in Table 1. An absorption maximum determined approximately from a bend in the curve is denoted by ~.

EXPERIMENTAL

The condensation of aldehydes with substituted 3-oxo-2,3-dihydrothionaphthenes was carried out in analogy with [10, 11]. The substances obtained were purified by repeated recrystallization from suitable organic solvents (see Table 1). In all the cases investigated, repeated recrystallization of the mixture of stereoisomers yielded one of the stereoisomers in a pure or almost pure form. This was normally isomer A (see Table 1 for the physical properties). The only exception was 2-(p-nitrobenzylidene)-N-methyl-3-oxoindolenine (V), purification of which by recrystallization yielded what we assumed to be form B.

The isolation of form B was usually difficult. Work on chromatographic separation of the isomers, which we are continuing, has not yet given positive results. A light filter which would make it possible to displace the equilibrium of the photochemical isomerization completely toward the formation of the isomer B cannot always be found. An equilibrium in which both forms are present in solution in considerable amounts is normally established. Even the determination of λ_{\max} of form B under these conditions is often inaccurate, not to mention ϵ_{\max} . Therefore, in Table 2 we consider it more accurate to give a column of "absorption maximum of solution irradiated with light" and not " λ_{\max} of form B." On the other hand, the data in Table 2 on the absorption maxima of form A and the isosbestic point are quite accurate.

Compounds Nos. 1, 3, 5, and 8 were described previously (see Table 1 for literature). The following compounds are described for the first time: 2-benzylidene-6-ethoxy-3-oxo-2,3-dihydrothionaphthene (No. 2), 2-benzylidene-6-chloro-3-oxo-2,3-dihydrothionaphthene (No. 3), 2-(p-nitrobenzylidene)-6-ethoxy-3-oxo-2,3-dihydrothionaphthene (No. 6), 2-(p-nitrobenzylidene)-6-oxo-2,3-dihydrothionaphthene (No. 7), 2-(p-methoxybenzylidene)-3-oxo-2,3-dihydrothionaphthene (No. 9), 2-(p-methoxybenzylidene)-6-ethoxy-3-oxo-2,3-dihydrothionaphthene (No. 10), 2-(p-methoxybenzylidene)-6-chloro-3-oxo-2,3-dihydrothionaphthene (No. 11), 2-(p-methoxybenzylidene)-4,5-benzo-3-oxo-2,3-dihydrothionaphthene (No. 12), 2-(p-dimethylaminobenzylidene)-3-oxo-2,3-dihydrothionaphthene (No. 13), 2-(p-dimethylaminobenzylidene)-6-ethoxy-3-oxo-2,3-dihydrothionaphthene (No. 14), 2-(p-dimethylaminobenzylidene)-6-chloro-3-oxo-2,3-dihydrothionaphthene (No. 15), 2-(p-dimethylaminobenzylidene)-4,5-benzo-3-oxo-2,3-dihydrothionaphthene (No. 16), 2-furfurylidene-6-ethoxy-3-oxo-2,3-dihydrothionaphthene (No. 18), 2-furfurylidene-6-chloro-3-oxo-2,3-dihydrothionaphthene (No. 19), and 2-furfurylidene-4,5-benzo-3-oxo-2,3-dihydrothionaphthene (No. 20).

Preparation of 2-(p-nitrobenzylidene)-3-oxoindolenine. An indoxyl melt [12] was carefully dissolved in water with ice. The solution obtained was filtered rapidly into a solution of hydrochloric acid containing fine pieces of ice. The yellow precipitate of indoxyl was collected by filtration in a carbon dioxide atmosphere and washed with cold distilled water which had first been boiled and cooled in a CO_2 atmosphere. The green paste of indoxyl was rapidly transferred to a tube, which was immediately closed tightly with a rubber bung. Part of the indoxyl paste was dried for determining the water content of the paste.

A 3.02-g sample of p-nitrobenzaldehyde was added to 100 ml of alcohol heated to 75° and a solution of 2.66 g of indoxyl (4.65 g of aqueous paste) in 50 ml of alcohol and 5 ml of concentrated hydrochloric acid added. After the mixture had been heated at 75° for 10 min, the product was filtered from the hot reaction mixture. The dark brown precipitate obtained was dried (weight 2.95 g) and then added to 150 ml of acetic acid heated to 112°. After the mixture had been stirred, it was filtered in the hot state. The acetic acid-insoluble residue (weight 2.1 g) was extracted with 220 ml of acetone in a Soxhlet apparatus. Cooling and filtration of the extract yielded 1 g of a red precipitate with m.p. 269°. After three recrystallizations from acetone with the use of activated charcoal, the product had m.p. 273-274° (form A). Literature data: m.p. 274° [13]. The substance was insoluble in n-hexane. The absorption maximum in benzene was 467 mμ (ϵ $1.5 \cdot 10^{-4}$). After irradiation with diffuse daylight, the substance had λ_{\max} 480 mμ. The isobestic point was 489 mμ.

Preparation of 2-(p-nitrobenzylidene)-N-methyl-3-oxoindolenine. A solution of 1.93 g of N-methyl-3-acetoxyindol [14] in 100 ml of 75% aqueous alcohol was heated to 75° with stirring. A hot solution of 1.51 g of p-nitrobenzaldehyde in 25 ml of alcohol and 2.5 ml of concentrated hydrochloric acid was then added. After the mixture had been stirred at 75° for 10 min, the precipitate was collected. The yield after drying was 2.0 g (71%). After three recrystallizations from benzene, the substance had m.p. 214-215° (form B).

Found %: C 69.10, 68.92; H 4.55, 4.63; N 10.21, 10.22. $C_{16}H_{12}O_3N_2$. Calculated %: C 68.7; H 4.28; N 10.0.

A solution in n-hexane had λ_{\max} 500 mμ and after irradiation of the solution with light from an electric lamp through a ZhS-18 filter, λ_{\max} 470 mμ. The isobestic point lay at 483 mμ.

Preparation of solutions and measurement of spectra. A 0.400- to 0.600-mg sample of the substance was introduced into 100-ml (for substances with a molecular extinction of the order of $1-1.5 \cdot 10^{-4}$) or 250-ml (for substances with a higher molecular extinction) graduated flask. Two thirds of the required volume of n-hexane* was added and the mixture heated on a water bath for 15 min. The contents of the flask were cooled to 20°, diluted to the mark with n-hexane, and mixed thoroughly. As in all the previous part of the work, the cells were filled with solution in a weak red light. The spectra were measured on an automatic recording SF-2M spectrophotometer.

Irradiation of solutions. After measurement of the spectrum of a solution prepared in the dark, the cell with the solution was removed from the spectrophotometer and immediately placed in a photocolormeter or a tightly closed box with a window for a light filter. Most often it was simply placed close to a window. For displacement of the equilibrium toward the formation of the isomer B we used irradiation with blue light on an FÉK-M photocolormeter for 30 min or irradiation with daylight for 1-10 min. For a reverse displacement of the equilibrium toward the formation of the isomer A, the solution was irradiated with light from a 109 W electric lamp through an OS-11 or ZhS-18 light filter for 10-30 min. After irradiation, the cell was placed in the spectrophotometer and the spectrum measured again.

SUMMARY

1. Phototropy of solutions is a general property among substituted 2-benzylidene-3-oxo-2,3-dihydrothionaphthenes.
2. Phototropic changes are also undergone by solutions of 2-(p-nitrobenzylidene)-3-oxoindolenine and 2-(p-nitrobenzylidene)-N-methyl-3-oxoindolenine.
3. Some preliminary conclusions on the effect of structure on color are given.

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HYDROGENATION OF UNSATURATED COMPOUNDS IN THE PRESENCE OF COLLOIDAL PALLADIUM

XV. HYDROGENATION OF SOME OXYGEN-CONTAINING ACETYLENE COMPOUNDS

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Continuing our investigations on the hydrogenation of unsaturated compounds in the presence of colloidal palladium, we hydrogenated propargyl alcohol, methylacetylenylcarbinol, propiolic acid, its ethyl ester, acetylacetylene, methylacetylene, and ethylacetylacetylene in methanol, ethanol, or ethyl ether. The hydrogenation of the methyl ether of dimethylacetylenylcarbinol was studied again.

Exhaustive hydrogenation of propargyl alcohol showed that in contrast to the tertiary alcohols we studied previously [1, 2], it adds hydrogen very slowly and peculiarly: Only 35% of the calculated amount of hydrogen was added in the first 6 hours, and after this the reaction rate increased sharply and then fell again (Fig. 1, curve 2). The hydrogenation was repeated many times, but the nature of the hydrogenation rate curve remained as before. A check of the catalyst on other compounds showed that it had the normal high activity. This curve of the hydrogenation rate is reminiscent of processes we observed previously and which proceed in the presence of certain retarders [1-3], and therefore there is the possibility that this type of hydrogenation is not a specific property of propargyl alcohol, but is produced by traces of some impurities from which the propargyl alcohol cannot be freed by repeated distillation.

Hydrogenation of propargyl alcohol with an equimolecular amount of hydrogen (partial hydrogenation) in the presence of colloidal palladium showed that the process is extremely selective and forms allyl alcohol.

A secondary acetylenic alcohol, methylacetylenylcarbinol, hydrogenated much more rapidly, and as the curve of the hydrogenation rate (Fig. 1, 1) shows, the process proceeded with gradual acceleration which was particularly strong in the second half of the reaction. Partial hydrogenation of this alcohol was also selective. Thus, as regards the selectivity of hydrogenation, the alcohols we investigated are similar to other acetylenic alcohols with a terminal acetylenyl group [1-4].

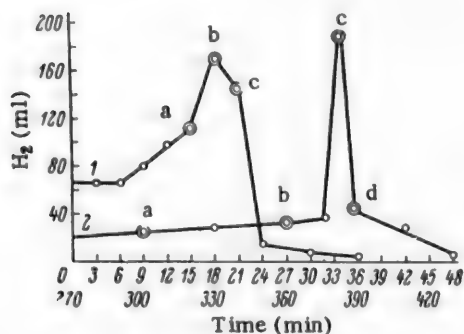


Fig. 1. Hydrogenation rate curves. 1) Methylacetylenylcarbinol, 2) propargyl alcohol (along the abscissa: upper scale for 1, lower scale for 2). Amount of hydrogen absorbed from the beginning of the process (in % of $2H_2$), 1: a) 47.0, b) 66.0, c) 82.0; 2: a) 26.0, b) 35.0, c) 66.0, d) 72.0.

It is interesting to note that in contrast to tertiary alcohols of analogous structure [4], some primary acetylenic alcohols, for example pent-3-yn-1-ol [5] and 1-phenylprop-1-yn-3-ol [6], which have a triple bond in the middle of the chain, are also hydrogenated selectively to the corresponding ethylenic alcohols in the presence of palladium [5, 6].

The hydrogenation of propiolic acid in the presence of various catalysts, including palladium, has been studied [7], while on the contrary there are few data on the esters of acetylenic acids. In particular, there is no information on the hydrogenation of ethyl propiolate in the presence of palladium.

The propiolic acid was prepared from fumaric acid and had constants which corresponded to literature data [8]. Ethyl propiolate was prepared by keeping a solution of the acid in anhydrous alcohol with concentrated sulfuric acid for 2 days. It had constants corresponding to literature data [8].

The hydrogenation rate of propiolic acid differed sharply, depending on the solvent. In absolute ether, the first molar equivalent of hydrogen was added in 190 min. During hydrogenation in methanol, the first phase of the reaction was complete in 15 min. The process in both solvents proceeded with acceleration, which was particularly strong in the second stage of hydrogenation (Fig. 2). In the partial hydrogenation of propiolic acid in absolute ether with a small amount of hydroquinone added (to prevent polymerization of the hydrogenation products), a liquid with the physical constants of acrylic acid (80% yield) was isolated from the hydrogenation product. In addition, a sample of the hydrogenation products did not give a precipitate with an ammonia solution of cuprous chloride, in contrast to propiolic acid itself; the infrared spectrum of propiolic acid contained the triple bond frequency of 2120 cm^{-1} , which is very strong with a layer thickness of $2\text{--}3\text{ }\mu$. The substance extracted from the hydrogenation product did not show this frequency even with a layer thickness of $50\text{ }\mu$. The spectra contained the frequency 1642 cm^{-1} (high intensity), which is characteristic of a terminal vinyl group.

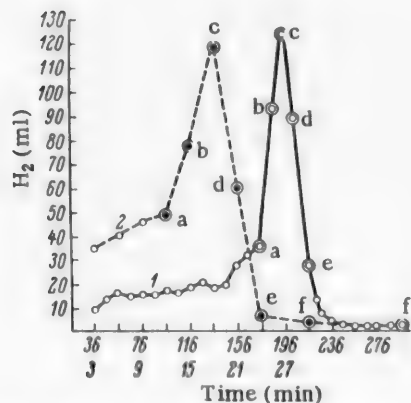


Fig. 2. Hydrogenation rate curves of propiolic acid. 1) In absolute ether, 2) in methanol (along the abscissa: upper scale for 1, lower scale for 2). Amount of hydrogen absorbed from the beginning of the process (in % of 2H_2): 1: a) 32.2, b) 42.2, c) 55.7, d) 65.2, e) 68.2, f) 71.4; 2: a) 32.3, b) 46.7, c) 69.5, d) 81.0, e) 82.4, f) 84.2.

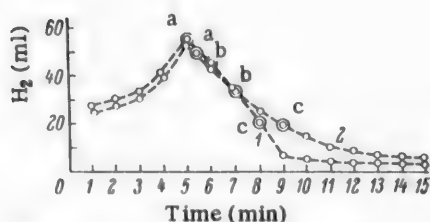


Fig. 3. Hydrogenation rate curves of ethyl propiolate. 1) Without hydroquinone, 2) with hydroquinone. Amount of hydrogen absorbed from the beginning of the process (in % of 2H_2): a) 48.9, b) 65.2, c) 74.1.

Ethyl propiolate was hydrogenated in methanol. The presence or absence of a small amount of hydroquinone did not affect the course of the hydrogenation or the composition of the hydrogenation product. The process proceeded at an increasing rate (Fig. 3) and this was particularly marked during the absorption of 35–60% of hydrogen (of 2H_2). Partial hydrogenation of ethyl propiolate yielded ethyl acrylate: In contrast to the starting material, the hydrogenation product did not give a precipitate either with an ammonia solution of silver oxide or with cuprous chloride. Thus, it was shown that propiolic acid and its ethyl ester are hydrogenated strictly selectively, but at different rates. The hydrogenation rate of propiolic acid depended strongly on the solvent.

In the literature there is a report that partial hydrogenation of liquid acetylacetylene on a nickel catalyst at 10–15 atm gives a good yield of methyl vinyl ketone [9]. Bourguet [6], who described the hydrogenation of two acetylenyl ketones in the presence of colloidal palladium, reported that he was unable to isolate a pure compound from the partial hydrogenation product of methylacetylacetylene. The other ketone he studied, namely phenylacetylacetylene, gave a mixture of the starting, ethylenic, and saturated ketones on partial hydrogenation.

We hydrogenated three acetylenyl ketones, namely acetylacetylene, methylacetylacetylene, and ethylacetylacetylene. Exhaustive hydrogenation in methanol with a small amount of hydroquinone (to prevent polymerization) proceeded differently for them (Fig. 4). The hydrogenation rate of the first ketone increased sharply after the absorption of one molar equivalent of hydrogen. On the other hand, the hydrogenation of the other two ketones proceeded more rapidly in the first half, and more slowly in the second half. Partial hydrogenation of the ketones was selective and led to the predominant formation of the corresponding ethylenic ketones.

In our work [10] we noted a sharp difference between the hydrogenation rates of methyl ethers of dimethylacetylenyl- and dimethylvinylcarbinols on the one hand and the ethyl ethers of dimethyl- and methylethylacetylenylcarbinols, on the other. As we synthesized the first two ethers from methyl iodide and the corresponding alcoholate, we suspected that the reason for the very slow hydrogenation of these ethers could have been the presence of small residues of iodine compounds.* To check this hypothesis, we resynthesized the methyl ether of

* The molecular concentration of $\text{KI} \cdot \text{I}_2$ poisoning a platinum catalyst in the decomposition of hydrogen peroxide is $1:5,000,000$ [11].

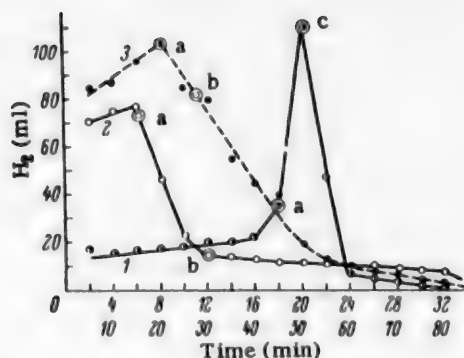


Fig. 4. Hydrogenation rate curves of acetylenyl ketones. 1) Acetylacetylene, 2) methylacetylacetylene, 3) ethylacetylacetylene (along the abscissa: upper scale for 2 and 3, lower scale for 1). Amount of hydrogen absorbed from the beginning of the process (in % of $2H_2$): a) 50.0, b) 66.3, c) 82.0.

TABLE 1

Time (min)	60	120	180	240	300	360	377	382	389	409	484
Amount of hydrogen absorbed from the beginning of the process	35 4.8	60 8.3	95 13.1	137 18.9	192 26.1	260 35.2	297 40.2	485 65.7	530 71.8	560 75.9	580 78.7

Footnote: The upper figure is the amount in milliliters and the lower figure, the percent of $2H_2$. 0.8680 g of propargyl alcohol, 3 ml of colloidal palladium (5 mg of Pd), 50 ml of methanol, 18° (764 mm); calculated amount of hydrogen ($2H_2$) = 736 ml.

2. Synthesis and hydrogenation of methylacetylenylcarbinol. The alcohol was prepared from 22 g of acetaldehyde and acetylene in 150 ml. of absolute ether in the presence of 75 g of dry powdered potassium hydroxide and 20 g of sodamide [13]. The yield was 10 g (30%).

B.p. $108-109^\circ$, d_{40}^{20} 0.8848, n_D^{20} 1.4260. Literature data [12]: b.p. $107-109^\circ$, d_{40}^{20} 0.8858, n_D^{20} 1.4265.

Data on the hydrogenation rate of methylacetylenylcarbinol are given in Fig. 1. We used 1.2960 g of the acetylenic alcohol, 3 ml of colloidal palladium (5 mg of Pd), and 50 ml of methanol at 17° (752 mm). Calculated: $2H_2$ = 890 ml. The hydrogenation (absorption of 85.4% of the hydrogen) was complete after 36 min.

For the partial hydrogenation of methylacetylenylcarbinol we used 0.9770 g of the substance, 3 ml of colloidal palladium (3 mg of Pd), and 50 ml of methanol at 17° (752 mm). Calculated: $1H_2$ = 335 ml. The hydrogenation time was 10 min. Heating a sample of the hydrogenation product with metallic sodium did not show the formation of acetylene [14]. The bromide-bromate method showed that the hydrogenation products contained 83% of a compound with a double bond.

*V. A. Kormer, A. A. Ryabkova, and N. A. Borovikova helped with the experimental work.

**After two distillations the alcohol had b.p. $113-114^\circ$, d_{40}^{20} 0.9725, n_D^{20} 1.4308. Literature data [12]: b.p. $114-115^\circ$, d_{40}^{20} 0.9715, n_D^{20} 1.4306.

dimethylacetylenylcarbinol not through the alcoholate, but from the acetylenic alcohol and methanol in the presence of concentrated sulfuric acid in the same way that we synthesized the ethyl ethers [10]. The methyl ether obtained, which had physical constants corresponding to literature data [12], was hydrogenated as fast as the ethyl ethers of acetylenic alcohols, and this apparently confirms the hypothesis put forward on the strong retarding action of iodine compounds on catalytic hydrogenation.

EXPERIMENTAL *

1. Hydrogenation of propargyl alcohol.** Data on the hydrogenation rate are given briefly in Table 1 and Fig. 1.

For the partial hydrogenation of propargyl alcohol we used 0.97 g of alcohol, 3 ml of colloidal palladium (5 mg of Pd), and 50 ml of methanol at 19° (770 mm). Calculated: $1H_2$ = 442 ml. This amount of hydrogen was absorbed in 5 hr. After hydrogenation, the solution did not give a precipitate with an ammonia solution of silver oxide or cuprous chloride.

TABLE 2

Time (min)		96 3	146 6	166 9	178 12	186 15	196 18	206 21	216 24	246 30	266 40	286 45
Amount of hydrogen absorbed from the beginning of the process	ml	108 35	204 75	265 122	301 170	395 248	520 367	610 427	638 434	655 440	662 444	668 446
	% of $2H_2$	11.6 6.6	21.8 14.2	28.3 23.2	32.2 32.3	42.2 46.7	55.7 69.5	65.2 81.0	68.2 82.4	69.9 83.6	70.6 84.2	71.2 84.6

Footnote: 1) 1.3322 g of propiolic acid, 40 ml of absolute ether, 5 ml of colloidal palladium (5 mg of Pd), and 18° (755 mm). Calculated: $2H_2 = 935$ ml (upper scale).
 2) 0.8232 g of propiolic acid, 40 ml of methanol, 3 ml of colloidal palladium (3 mg of Pd), and 19° (760 mm). Calculated: $2H_2 = 527$ ml (lower scale).

3. Preparation and hydrogenation of propiolic acid. From 100 g of fumaric acid* and 138 g of bromine with successive dehydrobromination, decarboxylation of the acid potassium salt, treatment with sulfuric acid, extraction, drying, and distillation yielded 7 g of propiolic acid with b.p. 71-72° (40 mm), $d_{20}^{20} 1.1436$, $n_D^{20} 1.4307^{**}$, which corresponds to literature data.

The acid was hydrogenated in absolute ether and methanol. Data on the hydrogenation rate are given briefly in Table 2 and Fig. 2.

For the partial hydrogenation of propiolic acid we used 21.6050 g of the substance, 20 ml of colloidal palladium (20 mg of Pd), and 150 ml of absolute ether at 21° (765 mm). Calculated: $1H_2 = 7600$ ml. A small amount of hydroquinone was added to prevent polymerization in the solution. The total hydrogenation time was 10 hr. In the initial period of the reaction, the mean absorption rate was 120 ml of hydrogen in 30 min. A fresh portion of catalyst, namely 10 ml of a concentrated colloidal solution of palladium (3 mg per ml), was added to the solution to accelerate the process. The initial hydrogenation rate was increased by a factor of almost five. After the absorption of 1/3 of the calculated amount of hydrogen (of $2H_2$), the reaction rate was again increased: The hydrogen absorption rate was increased from 200 to 550 ml per 10 min.

After the addition of the calculated amount of hydrogen (7600 ml), the reaction was stopped and the catalyst removed by filtration. The filtrate was dried over anhydrous sodium sulfate, the ether removed by distillation on a column, and the residue fractionated in vacuum (30 mm). The bulk of the material had b.p. 61-62° (30 mm), $d_{20}^{20} 1.0504$, $n_D^{20} 1.4220$. The yield of acrylic acid was 17.3 g (80%).

4. Preparation and hydrogenation of ethyl propiolate. To a solution of 9.5 g of propiolic acid in 20 ml of anhydrous alcohol was added 1.6 ml of concentrated sulfuric acid with external cooling. After standing for two days, the mixture was diluted with water and the ethyl propiolate formed extracted with ether, washed with bicarbonate, dried with calcium chloride, and distilled on a column. We collected a fraction (5.9 g) with b.p. 119-120° (758 mm), $d_{20}^{20} 0.9523$, $n_D^{20} 1.4092$.

Data on the hydrogenation rate of ethyl propiolate are given in Fig. 3. We used 0.7695 g of ethyl propiolate for hydrogenation without hydroquinone and 0.8040 g with a small amount of hydroquinone in addition to 40 ml of methanol and 2 ml of colloidal palladium (2 mg of Pd) at 17° (758 mm). Calculated: $2H_2 = 376$ and 396 ml. In both cases hydrogenation was complete in approximately 30 min.

For partial hydrogenation of ethyl propiolate we used 0.9758 g of the substance, 40 ml of methanol, and 2 ml of colloidal palladium (2 mg of Pd) at 18° (741 mm). Calculated: $1H_2 = 251$ ml. The calculated amount of hydrogen was absorbed in 7 min. The coagulated catalyst was removed by filtration and the precipitate on the filter washed with methanol. The completely transparent filtrate did not give a precipitate either with an ammonia solution of silver oxide or with cuprous chloride. This indicates that there was selective hydrogenation of ethyl propiolate to ethyl acrylate.

* Replacement of fumaric acid by maleic acid reduced the yield of dibromosuccinic acid by a factor of almost two.

** The values given in [15] were $n_D^{20} 1.43100$, $n_D^{25} 1.43316$.

5. The hydrogenation of acetylenyl ketones* was carried out in the presence of small amounts of hydroquinone to prevent polymerization. Data on the hydrogenation rate of acetylacetylene are given by curve 1 of Fig. 4; we used 0.4962 g of acetylacetylene, 3 ml of colloidal palladium (3 mg of Pd), and 50 ml of methanol at 19° (734 mm). Calculated: $2H_2 = 555$ ml. The hydrogenation was complete in 70 min. An analogous picture was observed with a somewhat larger sample of ketone (0.7075 g) and a larger amount of palladium (5 mg of Pd).

The partial hydrogenation of acetylacetylene was carried out with 0.7300 g of ketone in 50 ml of methanol and 3 ml of colloidal palladium (3 mg of Pd) at 19° (764 mm). The calculated amount of hydrogen (256 ml) was added after 65 min. Qualitative reactions showed that the hydrogenation product did not contain compounds with a terminal acetylenyl grouping, which indicates the selective nature of the hydrogenations.

Data on the hydrogenation rate of methylacetylacetylene are given by curve 2 in Fig. 4; we used 0.8140 g of methylacetylacetylene, 1 ml of colloidal palladium (1 mg of Pd), and 50 ml of methanol at 18° (784 mm). Calculated: $2H_2 = 460$ ml. Hydrogenation was practically complete in 50 min.

Partial hydrogenation of methylacetylacetylene was carried out with 2.5335 g of ketone in 50 ml of methanol and 2 ml of colloidal palladium (2 mg of Pd) at 18° (782 mm). The calculated amount of hydrogen (720 ml) was added in 22 min. Redistillation of the hydrogenation products yielded 1.35 g (53%) of a colorless liquid with a weak fruity odor, which became sharp during brief storage. The liquid had b.p. 122-123°, $d_{20}^{20} 0.8654$, and $n_D^{20} 1.4365$, which corresponds to literature data for pent-2-en-4-one and indicates the selectivity of the process.

Data on the hydrogenation rate of ethylacetylacetylene are given by curve 3 of Fig. 4; we used 1.5500 g of ethylacetylacetylene, 75 ml of methanol, and 3 ml of colloidal palladium solution (3 mg of Pd) at 18° (783 mm). Calculated: $2H_2 = 742$ ml. The hydrogenation was complete in 38 min.

SUMMARY

1. The hydrogenation of acetylenic alcohols (primary and secondary), acids, their esters, ketones, and ethers in the presence of colloidal palladium was studied.
2. It was established that the alcohols studied, propiolic acid, its ethyl ester, and also acetylenyl ketones with the triple bond at the end and in the center of the chain are hydrogenated strictly selectively at the acetylenic bond.
3. It was shown that the curves of the hydrogenation rate of primary and secondary acetylenic alcohols differ from each other and also from curves of the hydrogenation rates of tertiary alcohols.
4. Hydrogen is added to propiolic acid in absolute ether much more slowly than in methanol. The hydrogenation of the acid and its ethyl ester proceeds with acceleration, which is particularly strong in the second phase of the process.
5. Curves of the hydrogenation rate of acetylenyl ketones differ: Acetylacetylene is hydrogenated much more slowly than ketones with the acetylenic bonds in the middle of the chain. In addition, the hydrogenation rate of the first ketone increases sharply in the second stage, while, on the other hand, that of the other two ketones increases in the first phase.
6. The carbonyl group of the ketones, like the carboxyl and ester groups, was not hydrogenated under the conditions used.
7. It was established that the methyl ethers of dimethylacetylenyl- and dimethylvinylcarbinols obtained with methyl iodide are hydrogenated in the presence of colloidal palladium much more slowly than the alcohols themselves and the same ethers synthesized without the use of methyl iodide. This may be because of the presence of traces of iodine compounds in the ethers.

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SYNTHESIS AND CONVERSIONS OF UNSATURATED ORGANOSILICON COMPOUNDS

VIII. SYNTHESIS AND PROPERTIES OF SOME DITERTIARY γ -SILICON-CONTAINING ACETYLENIC GLYCOLS

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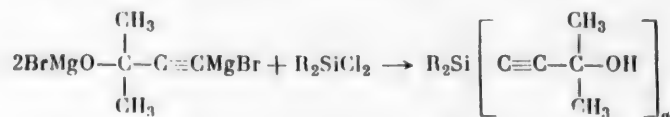
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In a previous investigation [1, 2] we studied the reaction of dimagnesiobromodimethylethynylcarbinol with dialkyl(aryl)dichlorosilanes in the presence of catalytic amounts of cuprous chloride and mercuric chloride according to the scheme



The presence of two hydroxyl groups in the ditertiary γ -silicon-containing acetylenic glycols obtained was demonstrated by the preparation of the corresponding acetyl derivatives.

In the present communication we describe the synthesis by the above method of other branched ditertiary γ -silicon-containing acetylenic glycols, whose structures were also demonstrated by the preparation of the corresponding acetyl derivatives [3]. The data are given in the table.

EXPERIMENTAL

1. Bis-(3-trimethylpent-1-yn-3-ol)-dimethylsilane (I). With continuous stirring and cooling, 49 g (0.5 mole) of methylethylacetylenylcarbinol was added to the Grignard reagent from 24 g of magnesium and 109 g of ethyl bromide and the reaction mixture then stirred for 3 hr and left overnight. On the following day a mixture of catalysts (0.5 g of HgCl_2 and 1.0 g of Cu_2Cl_2) was added to the reaction mixture and 34 g (0.25 mole) of dimethylchlorosilane introduced dropwise with cooling. The reaction mixture was stirred for 3 hr at room temperature and 6 hr on a water bath. The complex was decomposed with dilute hydrochloric acid (10-12%). The ether layer was separated and dried with sodium sulfate, the ether removed, and the residual product crystallized. The yield was 35 g (55.5%).

The other five ditertiary γ -silicon-containing acetylenic glycols whose characteristics are given in the table were prepared analogously.

2. Bis-(trimethylpent-1-yn-3-acetoxy)-dimethylsilane (VII). To 5.06 g of bis-(trimethylpent-1-yn-3-ol)-dimethylsilane was added 4.06 g of acetic anhydride. The mixture was heated for 8 hr at 70°. Removal of the acetic acid and two distillations yielded 2.35 g (33%) of the acetoxy derivative.

The other four acetyl derivatives of ditertiary γ -silicon-containing acetylenic glycols whose characteristics are given in the table were prepared analogously.

SUMMARY

1. The following six ditertiary γ -silicon-containing acetylenic glycols were synthesized and described for the first time: bis-(3-methylpent-1-yn-3-ol)-dimethylsilane, bis-(3-methylpent-1-yn-3-ol)-methylethylsilane, bis-(3-methylpent-1-yn-3-ol)-methylpropylsilane, bis-(3,5-dimethylhex-1-yn-3-ol)-dimethylsilane, bis-(3-methylhept-1-yn-3-ol)-dimethylsilane, and bis-(3-methylhept-1-yn-3-ol)-diethylsilane.

(continued overleaf)

Com- pound No.	Formula	Name	Boiling point (pres- sure in mm)
(I)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \\ \text{OH} \end{array} \right)_2 \text{Si}(\text{CH}_3)_2$	Bis-(3-methylpent-1-yn-3-ol)-dimethylsilane	M.p. 85.5—87°
(II)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \\ \text{OH} \end{array} \right)_2 \text{Si}(\text{CH}_3)(\text{C}_2\text{H}_5)$	Bis-(3-methylpent-1-yn-3-ol)-methylethylsilane	M.p. 60
(III)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \\ \text{OH} \end{array} \right)_2 \text{Si}(\text{CH}_3)(\text{C}_3\text{H}_7)$	Bis-(3-methylpent-1-yn-3-ol)-methylpropylsilane	M.p. 50—51
(IV)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \quad \\ \text{CH}_3 \quad \text{OH} \end{array} \right)_2 \text{Si}(\text{CH}_3)_2$	Bis-(3,5-dimethylhex-1-yn-3-ol)-dimethylsilane	141—143 (4)
(V)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \\ \text{OH} \end{array} \right)_2 \text{Si}(\text{CH}_3)_2$	Bis-(3-methylhept-1-yn-3-ol)-dimethylsilane	147 (4)
(VI)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \\ \text{OH} \end{array} \right)_2 \text{Si}(\text{C}_2\text{H}_5)_2$	Bis-(3-methylhept-1-yn-3-ol)-diethylsilane	M.p. 70—71
(VII)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \\ \text{OCOCH}_3 \end{array} \right)_2 \text{Si}(\text{CH}_3)_2$	Bis-(3-methylpent-1-yn-3-acetoxy)-dimethylsilane	140—145 (4)
(VIII)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \\ \text{OCOCH}_3 \end{array} \right)_2 \text{Si}(\text{CH}_3)(\text{C}_2\text{H}_5)$	Bis-(3-methylpent-1-yn-3-acetoxy)-methylpropylsilane	156—158 (4)
(IX)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \quad \\ \text{CH}_3 \quad \text{OCOCH}_3 \end{array} \right)_2 \text{Si}(\text{CH}_3)_2$	Bis-(3,5-dimethylhex-1-yn-3-acetoxy)-dimethylsilane	169—171 (4)
(X)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \\ \text{OCOCH}_3 \end{array} \right)_2 \text{Si}(\text{CH}_3)_2$	Bis-(3-methylhept-1-yn-3-acetoxy)-dimethylsilane	174—176 (3)
(XI)	$\left(\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}-\text{C}\equiv\text{C} \\ \\ \text{OCOCH}_3 \end{array} \right)_2 \text{Si}(\text{C}_2\text{H}_5)_2$	Bis-(3-methylhept-1-yn-3-acetoxy)-diethylsilane	190 (2)

2. The presence of two hydroxyl groups in the ditertiary γ -silicon-containing acetylenic glycols was demonstrated by the preparation of their acetyl derivatives: bis-(3-methylprop-1-yn-3-acetoxy)-dimethylsilane, bis-(3-methylpent-1-yn-3-acetoxy)-methylpropylsilane, bis-(3,5-dimethylhex-1-yn-3-acetoxy)-dimethylsilane, bis-(3-methylhept-1-yn-3-acetoxy)-dimethylsilane, and bis-(3-methylhept-1-yn-3-acetoxy)-diethylsilane.

d_4^{20}	n_D^{20}	MR_D		Found (%)			Empirical formula	Calculated (%)		
		found	calculated	C	H	Si		C	H	Si
—	—	—	—	66.71	9.72	11.00	$C_{14}H_{24}O_2Si$	66.03	9.66	11.44
—	—	—	—	67.80	10.46	11.24	$C_{15}H_{26}O_2Si$	67.61	10.39	11.54
—	—	—	—	68.74	10.57	9.50	$C_{16}H_{28}O_2Si$	68.68	10.05	10.01
0.9226	1.4668	92.7	92.48	70.44	10.72	8.87	$C_{18}H_{32}O_2Si$	70.00	10.40	9.10
0.9303	1.4670	92	92.48	70.65	11.00	9.03	$C_{18}H_{32}O_2Si$	70.00	10.40	9.10
—	—	—	—	71.76	11.21	7.42	$C_{20}H_{36}O_2Si$	71.3	10.78	8.34
0.9690	1.4707	97.02	95.42	64.80	8.60	8.23	$C_{18}H_{28}O_4Si$	64.24	8.38	8.35
0.9450	1.4655	106.75	104.68	66.20	8.94	8.62	$C_{20}H_{32}O_4Si$	65.89	8.847	7.705
0.9625	1.4600	111.0	110.64	67.81	9.80	6.73	$C_{22}H_{36}O_4Si$	67.3	9.21	7.15
0.9641	1.4590	111.0	110.64	67.9	9.98	6.96	$C_{22}H_{36}O_4Si$	67.3	9.21	7.15
0.9632	1.4586	118	117.48	69.13	10.04	6.12	$C_{24}H_{40}O_4Si$	68.5	9.58	6.67

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ELECTROREDUCTION AS A METHOD OF INVESTIGATING PROTEIN REDUCTION OF SOME DIKETOPIPERAZINES

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The presence of cyclic peptides in proteins has made it necessary to develop new analysis methods which make possible the selective destruction of a peptide chain and ring. One such method of investigating proteins is electroreduction on a mercury cathode [1] under mild conditions (5% HCl, 15-20°), which makes it possible to determine the presence of diketopiperazines by their conversion to piperazines, which are stable to hydrolysis.

The electroreduction of diketopiperazines and peptides of the simplest amino-acid composition (glycine, alanine, valine, leucine, phenylalanine, and proline) has been described in the literature up to now [1, 2]. The presence of diketopiperazines in the structure of silk [3] made it necessary to reduce synthetic models of them. The following mixed anhydrides were reduced: glycyl, seryl, alanyl seryl, and glycyl tyrosyl and also the simple cyclic anhydrides seryl seryl and tyrosyl tyrosyl.

As the purpose of this investigation was the preparation of references for chromatography, the piperazines obtained by electroreduction were examined by paper chromatography and electrophoresis and characteristic derivatives, namely dipicrates, were prepared. We showed that the electroreduction of diketopiperazines by Gavrillov and Koperina's method forms only piperazines. The reduction of tyrosine anhydride to the piperazine at 15-20° and a concentration of the reduced substance of 0.05% (100 mg in 200 ml of 5% HCl) proceeded quantitatively. With an increase in the concentration of the reduced substance to 0.1% (100 mg in 100 ml of 5% HCl) at 15-25°, in addition to 2,5-di-p-hydroxybenzylpiperazine, two new substances, which we did not identify (detected chromatographically), were formed.

EXPERIMENTAL

I. Preparation of diketopiperazines. Serine anhydride was prepared according to E. Fischer's method [4] with slight modification from 6.5 g of the hydrochloride of the ethyl ester of serine, which was synthesized by Elliot's method [5] (m.p. 104-106°; according to literature data, 101-102 and 114° [5, 6]). The serine ester was heated with 3 ml of alcohol for 1 hr. The anhydride was recrystallized from a small amount of hot water. The product weighed 1.2 g and was chromatographically homogeneous ($R_f = 0.25$). The homogeneity of the anhydride was established by chromatography on Leningrad paper "chromatograph B" with a density of 85 in the solvent system n-butanol-water-acetic acid (4: 5: 1). The m.p. was 260-266°. According to literature data: for the cis-isomer m.p. 226°, for the trans-isomer, 270-280° [4].

Found %: N 15.65, 15.91. $C_6H_{10}O_4N_2$. Calculated %: N 16.09.

Alanyl seryl anhydride was obtained by Bergmann's method [7] from the ethyl ester of carbobenzoxyalanylserine. A 5.9-g sample of the ethyl ester of carbobenzoxyalanylserine, which was obtained by Boissonnas's method [8] from 5.35 g of carbobenzoxyalanine and 4.05 g of the hydrochloride of the ethyl ester of serine, was dissolved in 40 ml of alcohol; 3 ml of water, 2 ml of acetic acid, and 0.5 g of palladium black were added and the substance reduced by continuous shaking in a stream of hydrogen until CO_2 was absent from the emergent hydrogen (40 hr). After the reduction, the catalyst was removed by filtration. The filtrate, i.e., an alcohol solution of the acetate of the ethyl ester of alanylserine, was heated under reflux for 12 hours. The white crystalline precipitate which formed on cooling was collected and recrystallized from hot alcohol and then from hot water. The weight was 0.8 g. The substance was chromatographically homogeneous and had R_f 0.45 and m.p. 224°; according to literature data: m.p. 228° [9].

Found %: N 17.81, 17.90. $C_8H_{10}O_3N_2$. Calculated %: N 17.71.

Glycyl seryl anhydride was obtained by the procedure described above for alanyl seryl anhydride from 5 g of carbobenzoxyglycine and 4.05 g of the hydrochloride of the ethyl ester of serine. Since the ethyl ester of carbobenzoxyglycylserine is sparingly soluble in alcohol, its reduction by hydrogen on palladium was longer than that of the corresponding ester of carbobenzoxyalanylserine; the reduction was complete in 64 hr. The alcohol solution of the acetate of the ester of glycylserine was heated for 16 hr instead of 12 hr, as was the case of the acetate of the ester of alanylserine. Recrystallization from hot water yielded 0.4 g of product. The anhydride was chromatographically homogeneous and had R_f 0.29 and m.p. 227°; according to literature data: 220-227° [9].

Found %: N 19.55, 19.67. $C_8H_{10}O_3N_2$. Calculated %: N 19.44.

Glycyl tyrosyl anhydride was obtained in the same way as alanyl seryl anhydride from 5 g of carbobenzoxyglycine and 6.5 g of the hydrochloride of the methyl ester of tyrosine [10]. The methyl ester of carbobenzoxyglycyltyrosine was reduced by hydrogen on palladium in 40 hr. The alcohol solution of the acetate of the ester of glycyltyrosine was heated for 8 hr. The anhydride obtained in this way was recrystallized from hot water with the addition of a few drops of acetic acid. The product weighed 1.5 g and had m.p. 284°; according to literature data: 295° [10]. It was chromatographically pure and R_f 0.63.

Found %: N 12.51, 12.22. $C_{11}H_{12}O_4N_2$. Calculated %: N 12.72.

Tyrosine anhydride was synthesized by the method of E. Fischer [10]. After recrystallization from hot ammonia solution, the anhydride was chromatographically homogeneous and had R_f 0.77 and m.p. 277-280°; according to literature data: 277-280° [10].

Found %: N 8.48, 8.78. $C_{11}H_{12}O_4N_2$. Calculated %: N 8.58.

II. Electroreduction of diketopiperazines. The electroreduction of the anhydrides was carried out in the apparatus described previously [11] with a rotating mercury cathode in a mixture of hydrochloric and acetic acids. The volume of mercury was 40-50 ml, the cathode current density 0.056 amp/cm², the volume of the cathode solution 200 ml, the temperature of the cathode liquid 15-20°, and the hydrochloric acid concentration 5%. The weight of the substance reduced did not exceed 100 mg. The reduction lasted for 5-7 hr. The dc voltage was 120 v and the current strength 5 amp. Redistilled hydrochloric acid was used. The mercury was purified and redistilled in vacuum. The piperazines were chromatographed with the following solvent systems:

1) n-Butanol-water-acetic acid in the ratios of 4:5:1 or 5.0:1.5:3.5; 2) pyridine-water-formic acid in the ratio 5:1.5:3.5. The electrophoresis was carried out in 30% acetic acid with a potential gradient of 6.1 v/cm. The chromatograms were developed with benzidine [12].

Electroreduction of serine anhydride. A 100-mg sample of serine anhydride was dissolved in 30 ml of hot distilled water, and then 50 ml of water, 80 ml of acetic acid, and 40 ml of 20% redistilled HCl were added. After the reduction, the cathode solution was evaporated to dryness in vacuum on a water bath at a temperature of no higher than 30°. The dry residue was dissolved in a small amount of water and chromatographed. Serine, serine anhydride, and 2,5-dihydroxymethylpiperazine were detected on a chromatogram and an electrophoregram. Then 10 ml of concentrated hydrochloric acid was added to the aqueous solution of the dry residue and the solution heated at 115-120° on a glycerol bath for 24 hr. The hydrolyzate was evaporated to dryness in vacuum and dissolved in 10 ml of water. Serine and 2,5-dihydroxymethylpiperazine [R_f = 0.64 in pyridine, 0.07 in butanol (50:15:35), v = 3.17 cm/hr] were detected on a chromatogram and electrophoregram of the hydrolyzate.

Preparation of dipicrate. To 10 ml of an aqueous solution of the hydrolyzate of the reduced serine anhydride was added 10 ml of a saturated aqueous solution of picric acid and the mixture heated to boiling. The fine, bright yellow crystals which precipitated on cooling were collected, washed with water, alcohol, and ether, and recrystallized from hot water. The weight of the chromatographically and electrophoretically pure dipicrate of 2,5-dihydroxymethylpiperazine was 90 mg. The dipicrate darkened at 200° and melted at 250° (with strong decomposition).

Found %: C 35.60, 35.80; H 3.55, 3.16; N 18.41, 18.26. $C_{18}H_{20}O_{16}N_8$. Calculated %: C 35.76; H 3.33; N 18.54.

Electroreduction of glycyl seryl anhydride. A 100-mg sample of the anhydride was reduced in the same way as serine anhydride. A chromatogram of the cathode liquid before hydrolysis showed glycine, serine, glycyl seryl anhydride (traces), and 2-hydroxymethylpiperazine. A chromatogram of the hydrolyzate of the cathode liquid (the hydrolysis conditions were given above and the hydrolysis time was 10 hr) showed glycine, serine, and 2-hydroxymethylpiperazine ($R_f = 0.54$ in pyridine, $v = 3.62$ cm/hr).

The dipicrate of 2-hydroxymethylpiperazine was obtained by the method described above. The addition of picric acid to an aqueous solution of the hydrolyzate of reduced glycyl seryl anhydride immediately precipitated lustrous light yellow crystals (platelets). The weight of the chromatographically and electrophoretically homogeneous dipicrate of 2-hydroxymethylpiperazine was 108 mg. The dipicrate darkened at 230° and melted at 310° (strong decomposition).

Found %: C 35.49, 35.60; H 3.28, 3.22; N 19.47, 19.52. $C_{17}H_{18}O_{15}N_8$. Calculated %: C 35.54; H 3.16; N 19.51.

Electroreduction of alanyl seryl anhydride. A 100-mg sample of the substance was reduced by the method described above. A chromatogram and electrophoregram of the cathode liquid before hydrolysis showed serine, alanine, alanyl seryl anhydride (traces), and 2-methyl-5-hydroxymethylpiperazine. After hydrolysis (10 hr), serine, alanine and 2-methyl-5-hydroxymethylpiperazine ($R_f = 0.68$ in pyridine, $v = 3.38$ cm/hr) were detected (table).

Piperazines	R_f		v (cm/hr)
	50: 15: 35 pyridine — water — HCOOH	n-Butanol — water — CH ₃ COOH	
2,5-Dihydroxymethylpiperazine	0.64	0.07 (5.0:1.5:3.5)	3.17
2-Hydroxymethylpiperazine	0.54	—	3.62
2-Methyl-5-hydroxymethylpiperazine	0.68	—	3.38
2-p-Hydroxybenzylpiperazine	0.79	—	2.40
2,5-Di-p-hydroxybenzylpiperazine	—	0.49 (4:5:1)	1.40

The dipicrate of 2-methyl-5-hydroxymethylpiperazine was obtained in the same way as that of 2-hydroxymethylpiperazine. Fine, bright yellow crystals formed immediately after picric acid was added to an aqueous solution of the hydrolyzate of reduced alanyl seryl anhydride without heating. They had m.p. 315° and darkened at 220° ; the weight was 130 mg.

Found %: C 37.28, 37.31; H 3.55, 3.73; N 19.11, 18.96. $C_{18}H_{20}O_{15}N_8$. Calculated %: C 36.74; H 3.42; N 19.05.

Electroreduction of glycyl tyrosyl anhydride. A 100-mg sample of the anhydride was reduced by the method described above. Chromatograms and electrophoregrams of the cathode liquid before hydrolysis showed glycyl tyrosyl anhydride (traces) and 2-p-hydroxybenzylpiperazine. After hydrolysis (24 hr), glycine, tyrosine, and 2-hydroxybenzylpiperazine ($R_f = 0.79$ in pyridine, $v = 2.40$ cm/hr) were detected.

The dipicrate of 2-p-hydroxybenzylpiperazine was isolated by the method described for 2,5-dihydroxymethylpiperazine. An emulsion formed immediately after the addition of picric acid solution to an aqueous solution of 2-hydroxybenzylpiperazine and this coagulated on heating. The orange-yellow precipitate was collected and recrystallized from a mixture of water and acetic acid with heating. The dipicrate was chromatographically and electrophoretically homogeneous. It had m.p. 247° (strong decomposition) and darkened at 220° .

Found %: C 42.27, 42.50; H 3.60, 3.51; N 17.29, 17.03. $C_{23}H_{22}O_{15}N_8$. Calculated %: C 42.47; H 3.41; N 17.22.

Electroreduction of tyrosine anhydride. A 100-mg sample of the anhydride was reduced by the method described above. A chromatogram and electrophoregram of the cathode liquid before hydrolysis showed the presence of the anhydride (traces) and 2,5-di-p-hydroxybenzylpiperazine. After hydrolysis (60 hr), tyrosine and 2,5-di-p-hydroxybenzylpiperazine [$R_f = 0.49$ in butanol (4:5:1), $v = 1.40$ cm/hr] were detected.

The dipicrate of 2,5-di-p-hydroxybenzylpiperazine was obtained in the same way as the dipicrate of 2-p-hydroxybenzylpiperazine. The yellow precipitate was washed with water, a mixture of water and acetic acid, and again with water and recrystallized from a mixture of water and acetic acid (2: 1) with heating. It had m.p. 280° (strong decomposition).

Found %: C 47.80, 47.30, H 3.81, 3.90; N 14.98, 14.83. $C_{20}H_{25}O_{14}N_4$. Calculated %: C 47.62; H 3.73; N 14.81.

SUMMARY

The electroreduction of serine, glycyl seryl, alanyl seryl, glycyl tyrosyl and tyrosine anhydrides was investigated. It was shown that the electroreduction of these diketopiperazines on a mercury cathode forms only piperazines; and the R_f values on a chromatogram and rates of movement v on the electrophoregram of the latter were found.

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SYNTHESIS OF ESTERS OF ACYLATED AMINO ACIDS AND GLYCOLIC ACIDS

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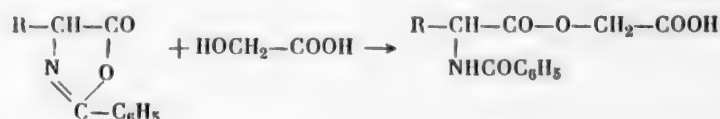
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 1, pp. 42-45,

January, 1961

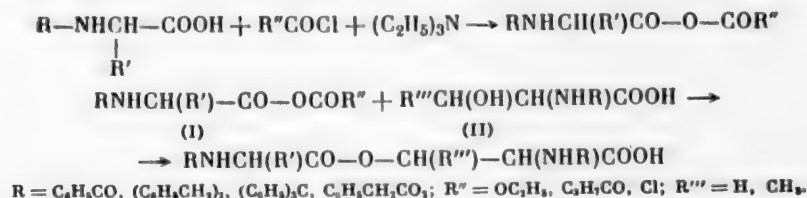
Original article submitted February 11, 1960

It was shown previously [1] that glycolic esters of benzoyl- and carbobenzoxy-D,L-amino acids react with esters of D,L-amino acids in the presence of chymotrypsin with the formation of esters of benzoyl- and carbobenzoxy-L-peptides. To study this reaction, we synthesized glycolic esters of benzoyl-D,L-leucine, D,L-valine, and D,L-alanine and carbobenzoxy-D,L- and D- and L-phenylalanine and carbobenzoxy-D,L-leucine.

The glycolic esters of the benzoylamino acids were prepared from the corresponding oxazolones by heating in ether with glycolic acid.



The glycolic esters of carbobenzoxyamino acids were prepared by the mixed anhydride method. The use of this method for the synthesis of derivatives of β -hydroxyamino acids was described previously [2-5].



An essential point in the synthesis is the choice of the most suitable conditions for the reaction of the mixed anhydrides [1] with the second "alcohol" component, in particular, with glycolic acid. The optimal synthesis conditions were found to consist of preparing the mixed anhydrides of acylated amino acids with chlorocarbonic ester in a ratio of 1:1 in the presence of 1 mole of triethylamine for 8 min at -8° in chloroform, methylene chloride, or tetrahydrofuran. Then 1.2 mole of glycolic acid was added in one portion at -12° . As the reaction with the hydroxyl group proceeded slowly, it was advantageous to leave the mixture overnight at 25° .

The synthesis of peptides through mixed anhydrides of amino acids is always accompanied by side reactions. The reaction of mixed anhydrides with the hydroxyl group of low activity was sometimes accompanied by the formation of considerable amounts of neutral compounds, which gave a hydroxamic acid reaction and were hydrolyzed by 0.01 N alkali on heating. These compounds could be separated comparatively readily by washing the triethylamine salt of the glycolic ester of the carbobenzoxyamino acid with absolute ether. The glycolic esters of benzoyl-amino acids were crystalline compounds, while the glycolic esters of carbobenzoxyamino acids were colorless vitreous oils. The compounds synthesized (which have not been described in the literature) and their yields and constants are given below.

Name (glycolic esters)	Yield (%)	Melting point
Benzoyl-D,L-phenylalanine	83	80—82° *
Benzoyl-D,L-leucine	77	137—138 *
Benzoyl-D,L-valine	70	130.5—131.5 *
Benzoyl-D,L-alanine	70	113.5—114.5 *
Carbobenzoxy-D,L-phenylalanine	85	—
Carbobenzoxy-D,L-leucine	83	—
Carbobenzoxy-L-phenylalanine	77	—
Carbobenzoxy-D-phenylalanine	77	—
Carbobenzoxy(O-benzoyl)-L-tyrosine	89.3	—

* From aqueous alcohol.

EXPERIMENTAL

Glycolic ester of benzoyl-D,L-leucine. An ether solution of 2-phenyl-4-isobutyl-5-oxazolone (from 8.3 g of benzoyl-D,L-leucine) and 3.4 g of glycolic acid was heated for 4 hr on a water bath and left for 12 hr at 20°. The ether was removed in vacuum and the residual oil triturated with water. The yield of the glycolic ester of benzoyl-D,L-leucine was 7.7 g.

Found %: C 61.44, 61.44; H 6.52, 6.51; N 4.90, 4.88. $C_{15}H_{19}O_5N$. Calculated %: C 61.44; H 6.48; N 4.77.

The glycolic ester of benzoyl-D,L-valine was obtained from 2.21 g of benzoyl-D,L-valine and 1 g of glycolic acid. The yield was 1.9 g.

Found %: C 60.54, 60.49; H 6.29, 6.23; N 5.02, 5.37. $C_{14}H_{17}O_5N$. Calculated %: C 60.22; H 6.09; N 5.02.

The glycolic ester of benzoyl-D,L-alanine was obtained from 1 g of benzoyl-D,L-alanine and 0.57 g of glycolic acid. The yield was 0.9 g.

Found %: C 57.39, 57.47; H 5.30, 5.39; N 5.75, 5.65. $C_{13}H_{15}O_5N$. Calculated %: C 57.39; H 5.17; N 5.78.

The glycolic ester of carbobenzoxy-D,L-phenylalanine. A cooled solution of 1.4 ml of chlorocarbonic ester in 2 ml of anhydrous chloroform was added with stirring to a solution of 4.4 g of carbobenzoxyphenylalanine and 2.2 ml of anhydrous triethylamine in 30 ml of anhydrous chloroform at -8°. The mixture was stirred for 8 min at -8° and then a solution of 1.35 g of glycolic acid and 2.64 ml of triethylamine in 30 ml of anhydrous chloroform added in one portion. The mixture was left for 12 hr in a thermostat at 25°. The solution was evaporated in vacuum and the residue, which consisted of a mixture of crystals and oil, was triturated repeatedly with absolute ether for the removal of high-molecular impurities and then dissolved in chloroform and the chloroform solution washed with 5 N HCl and several times with water and evaporated in vacuum. The glycolic ester of carbobenzoxy-D,L-phenylalanine was obtained as a clear, colorless oil, which was repeatedly evaporated with anhydrous benzene and left in a vacuum desiccator over P_2O_5 . The yield was 4.5 g and the product was soluble in organic solvents, slightly soluble in hot water, and insoluble in cold water. Methylene chloride and dioxane could be used as reaction solvents.

Found %: C 63.79; H 5.75. $C_{19}H_{19}O_6N$. Calculated %: C 63.86; H 5.32.

Determination of ester group. The glycolic ester of carbobenzoxy-D,L-phenylalanine was dissolved in 2 ml of alcohol and titrated with 0.01 N NaOH. Excess 0.01 N NaOH was added and the mixture left for 24 hr at ~20°. The excess alkali was titrated with 0.01 N sulfuric acid.

A 0.0109-g sample of the substance required 3.2 ml of 0.01 N NaOH for titration and 3.2 ml for hydrolysis; a 0.0156-g sample of substance required 4.23 ml of 0.01 N NaOH for titration and 4.28 ml for hydrolysis. Equiv. found 340.6, 368. $C_{19}H_{19}O_6N$. Equiv. calculated 357.

The glycolic ester of carbobenzoxy-D-phenylalanine was prepared from 0.5 g of carbobenzoxy-D-phenylalanine. The yield was 0.45 g and the substance consisted of a clear, colorless oil.

Equiv. found 383. $C_{19}H_{19}O_6N$. Equiv. calculated 357.

The glycolic ester of carbobenzoxy-L-phenylalanine was prepared from 0.5 g of carbobenzoxy-L-phenylalanine. The yield was 0.45 g.

Equiv. found 385. $C_{19}H_{19}O_6N$. Equiv. calculated 357.

Glycolic ester of carbobenzoxy-D,L-leucine. A mixed anhydride was prepared from 1 g of carbobenzoxy-D,L-leucine and 0.53 ml of triethylamine in 7 ml of chloroform at -12° , and after 8 min 0.43 g of glycolic acid and 0.8 ml of triethylamine in 10 ml of chloroform were added at -10 to -12° . The yield was 1 g and the substance was a colorless oil, which was soluble in organic solvents and insoluble in water.

Found %: C 58.09, 58.16; H 6.48, 6.62. Equiv. 327. $C_{18}H_{21}O_6N \cdot \frac{1}{2}H_2O$. Calculated %: C 57.82; H 6.64. Equiv. 323.

Glycolic ester of O-benzoyl-N-carbobenzoxy-L-tyrosine*. To 0.5 g of O-benzoyl-N-carbobenzoxy-L-tyrosine and 0.167 ml of anhydrous triethylamine in 7 ml of anhydrous chloroform was added 0.115 ml of cooled chloro-carbonic ester at -8° and after 8 min, 0.138 g of glycolic acid and 0.25 ml of triethylamine in 7 ml of chloroform. The reaction mixture was kept at 30° for 5 min and at $\sim 20^\circ$ for 12 hr. After evaporation of the chloroform in vacuum, the residue was repeatedly triturated with absolute ether, redissolved in chloroform, and washed with 2 N HCl and water. After evaporation of the solution, the residue was dried by repeated evaporation of the water with benzene. The residual oil was converted into an amorphous, very hygroscopic powder by trituration with ligroin. The yield was 0.5 g (89.3%).

Found %: C 62.54, 62.67; H 5.2, 5.28. Equiv. 468. $C_{28}H_{25}O_7N \cdot 2H_2O$. Calculated %: C 62.51; H 5.05. Equiv. 463.4.

SUMMARY

The synthesis of glycolic esters of benzoyl- and carbobenzoxyamino acids is described.

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* Synthesized by the student A. Mamedova.

CYCLIZATION OF PEPTIDES IN THE PRESENCE OF ETHOXYACETYLENE

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As already reported [1, 2], ethoxyacetylene may be used for the cyclization of peptides [3]. The cyclization was carried out in aqueous methanol (concentration from 1.2 to 2.5 mmole/liter) in the presence of excess ethoxyacetylene. The cyclopeptides obtained by this method are given in the table, which shows that cyclization occurred in yields of up to 48%. The cyclization temperature and reaction time had a substantial effect on the yield. A rise in temperature increased the yield and simultaneously decreased the reaction time (No. 1).

Compound No.	Starting peptide	Solution concentration (mmole/liter)	Ethoxyacetylene excess	Reaction time	Temperature	Cyclopeptide yield (%)
1	Glycylleucylglycylglycylleucylglycine [1]	{ a) 2 b) 1.7	{ 20-fold The same	{ 1 week 3 hr 12 hr 12 hr	{ 20° 40-45 60-70 20	{ 11.2 27.4
2	Glycylphenylalanylglycylglycylphenylalanylglycine [2]) 2	The same	1 month	20	48.5
3	Glycyl- ϵ -N-tosyllysylglycylglycyl- ϵ -N-tosyllysylglycine	{ a) 1.2 b) 1.2	{ 30-fold 10-fold	{ 10 hr 10 days 12 hr 24 hr	{ 60-70 20 60-70 20	{ 24 29.2
4	Glycyl- ϵ -N-tosyllysylglycine	2.4	4-fold	10 days	20	15.8
5	Valyl- ϵ -N-tosyllysylleucylvalyl- ϵ -N-tosyllysylleucine*	1.8	10-fold	{ 10 hr 12 hr	{ 60-70 20	{ 20.2
6	Glycylleucylglycylleucine*	{ a) 2.35 b) 1.8	{ 20-fold 4.5-fold	{ 15 days 12 hr 24 hr	{ 20 60-70 20	{ 24.6 36.9

*A detailed description of the cyclization of these peptides will be published later.

If the reaction time was increased, cyclization proceeded in good yield without heating at room temperature (No. 2). If the reaction mixture was heated at the beginning of the reaction, the subsequent storage time at room temperature did not affect the cyclopeptide yield (No. 3). In exactly the same way, the excess of ethoxyacetylene used for the reaction did not affect the yield (Nos. 3 and 6). When the tripeptide glycyl- ϵ -N-tosylglycylglycine was used for the reaction, it was impossible to obtain the corresponding cyclotriptide: Dimerization of the tripeptide molecule occurred during the reaction and the corresponding cyclohexapeptide was formed, and this agrees completely with the results we obtained previously [2] and with literature data [4].

It should be noted that with the use of ethoxyacetylene, the separation of the mixture of substances obtained after the reaction presented no difficulties as the by-product of the reaction was ethyl acetate. For separation of the cyclopeptide obtained from the starting linear peptide it was convenient to use preparative electrophoresis on cellulose powder [5]. This method is simpler than the methods usually used for isolation and purification (countercurrent distribution and chromatography on ion-exchange resins).

EXPERIMENTAL

ϵ -N-Tosyllysine was obtained by the method proposed for the preparation of δ -carbobenzoxy-L-ornithine [6]. A boiling solution of 9 g (0.05 mole) of lysine monohydrochloride in 75 ml of water was saturated with copper carbonate. The excess copper carbonate was removed by filtration after the solution had cooled. The filtrate was cooled to 0° and stirred while 50 ml of 2 N NaOH (0.1 mole) and a solution of 9.5 g (0.05 mole) of p-toluenesulfonyl chloride in 100 ml of acetone were added dropwise. Stirring was continued for a further 2 hr at 0° and 3 hr at ~20°. The blue precipitate of the copper complex of ϵ -N-tosyllysine was collected, washed with water and methanol, and dried in air. The dry powder was suspended in 200 ml of water and hydrogen sulfide passed into the suspension for 3 hr and then the flask with the reaction mixture left overnight. The suspension was boiled for 3-5 min and the copper sulfide precipitate separated on a hot filter funnel. The tosyllysine precipitated when the filtrate was cooled. We obtained 10.4 g (69.3%). After recrystallization from ethanol, the substance had m.p. 217-219°.

Found %: N 9.59, 9.20. $C_{13}H_{20}O_4N_2S$. Calculated %: N 9.33.

Hydrochloride of the methyl ester of ϵ -N-tosyllysine. A suspension of 8 g of ϵ -N-tosyllysine in 80 ml of anhydrous chloroform was saturated with dry hydrogen chloride. After saturation, the solution was filtered and evaporated to dryness in vacuum. The residue was dried over alkali in a vacuum desiccator. We obtained 9 g (96.7%) and the product had m.p. 146-147°. The substance was chromatographically homogeneous: R_f 0.65 (in the system 1-butanol: water: acetic acid, 4: 5: 1)*.

Found %: Cl 9.8. $C_{14}H_{23}O_4N_2SCl$. Calculated %: Cl 10.1.

Methyl ester of cbz**-glycyl- ϵ -N-tosyllysine. A 4.35-g sample (0.021 mole) of cbz-glycine and 7.3 g (0.021 mole) of the hydrochloride of the methyl ester of ϵ -N-tosyllysine were coupled by the method in [7] in 120 ml of anhydrous chloroform in the presence of 2.4 ml (0.025 mole) of ethyl chlorocarbonate and 6.35 ml (0.0458 mole) of triethylamine. The normal treatment of the reaction mixture gave 9.7 g (92.3%) of the ester as a colorless oil, whose purity was checked by paper electrophoresis [8] and which was then hydrolyzed without further treatment.

Cbz-glycyl- ϵ -N-tosyllysine. To a solution of 13.7 g (0.027 mole) of the methyl ester of cbz-glycyl- ϵ -N-tosyllysine in 60 ml of methanol was added 38 ml (0.038 mole) of 1 N NaOH and the reaction mixture left at ~20°. After 2.5 hr, the solution was diluted with an equal volume of water, filtered and acidified to Congo with 2 N HCl. The oil which separated crystallized on prolonged standing. We obtained 11.3 g (85.6%) of product with m.p. 135-136°. After reprecipitation from ethanol with water, the product had m.p. 139-140°.

Found: equiv. 497, 501. $C_{23}H_{29}O_7N_3S$. Calculated: equiv. 492.

Methyl ester of cbz-glycyl- ϵ -N-tosylsilylglycine. A 5.9-g sample (0.012 mole) of cbz-glycyl- ϵ -N-tosyllysine was dissolved in 30 ml of dioxane at 40-50°. The solution was cooled to ~20°, and 1.1 g (0.012 mole) of the methyl ester of glycine and 3 g (0.04 mole) of dicyclohexylcarbodiimide were added to it [9]. The reaction mixture was left for a day at ~20°. The precipitate of dicyclohexylurea was removed by filtration and washed with dioxane. The filtrate and wash solutions were evaporated to dryness in vacuum. The residue was dissolved in chloroform and the chloroform solution washed with 1 N HCl, 3% NaHCO₃ solution, and water, dried over baked sodium sulfate, and evaporated in vacuum. The residual oil crystallized on standing with ether. We obtained 5.5 g (81.6%) of product. After reprecipitation from ethanol with water, the product had m.p. 127-129°.

Found %: C 55.13; H 6.48; N 9.68. $C_{26}H_{34}O_8N_4S$. Calculated %: C 55.52; H 6.05; N 9.96.

Cbz-glycyl- ϵ -N-tosylsilylglycine. To a solution of 4.65 g (0.0082 mole) of the methyl ester of cbz-glycyl- ϵ -N-tosylsilylglycine in 40 ml of methanol was added 11.5 ml (0.0115 mole) 1 N NaOH and the reaction mixture

*All the R_f values given below were determined with the same solvent system (ascending chromatography).

**Cbz represents carbobenzoxy.

left at $\sim 20^\circ$. After 2.5 hr, the solution was diluted with water, filtered, and acidified to Congo with 5 N HCl. The oil which separated crystallized on standing. We obtained 4.1 g (91.3%) of product with m.p. 140-142°.

Found: equiv. 548.8. $C_{25}H_{32}O_8N_4S$. Calculated: equiv. 548.

Hydrochloride of methyl ester of glycyl- ϵ -N-tosyllysylglycine. To a solution of 3 g of the methyl ester of the cbz-tripeptide in 60 ml of methanol was added 5.3 ml of 1 N HCl and the mixture hydrogenated in the presence of palladium black. After reduction, the solution was separated from the catalyst and evaporated in vacuum. The residue was dried by vacuum distillation with anhydrous ethanol. Crystallization from a mixture of alcohol and ether yielded 2.1 g (85.3%) of substance with m.p. 198-199° (with decomp.); it was chromatographically homogeneous: R_f 0.64.

Methyl ester of cbz-glycyl- ϵ -N-tosyllysylglycylglycyl- ϵ -N-tosyllysylglycine. A 2-g sample (0.0036 mole) of cbz-glycyl- ϵ -N-tosyllysylglycine was coupled with 1.8 g (0.0036 mole) of the hydrochloride of the methyl ester of glycyl- ϵ -N-tosyllysylglycine in 40 ml of anhydrous chloroform in the presence of 0.4 ml (0.0043 mole) of ethyl chlorocarbonate and 1.2 ml (0.0086 mole) of triethylamine. The reaction mixture, which was kept at $\sim 20^\circ$ for 12 hr, was a gelatinous mass, which was diluted with ethyl acetate before treatment. The chloroform-ethyl acetate solution was treated in the usual way. The oil obtained crystallized when treated with a mixture of ether and acetone. We isolated 3 g (86.9%) of product with m.p. 92-94°. The substance was electrophoretically homogeneous.

Found %: C 53.22, 53.37; H 6.65, 6.68. $C_{43}H_{58}O_{13}N_8S_2 \cdot \frac{1}{2}H_2O$. Calculated %: C 53.35; H 6.10.

Cbz-glycyl- ϵ -N-tosyllysylglycylglycyl- ϵ -N-tosyllysylglycine. To a solution of 3 g (0.0031 mole) of the methyl ester of the cbz-hexapeptide in 30 ml of methanol was added 4.3 ml of 1 N NaOH and the reaction mixture left at $\sim 20^\circ$ for 8 hr. The solution was filtered and acidified to Congo with 2 N HCl; the methanol was removed in vacuum. The residual oil was dissolved in anhydrous ethanol and the solution evaporated to dryness in vacuum. The residue was treated several times with anhydrous ethanol and acetone with the solvents removed in vacuum each time. We obtained 2.5 g (85.3%) of a dry, amorphous, foamy substance; it was electrophoretically homogeneous.

Found %: N 11.52, 11.52; equiv. 984. $C_{42}H_{56}O_{13}N_8S_2$. Calculated %: N 11.87; equiv. 944.

Glycyl- ϵ -N-tosyllysylglycylglycyl- ϵ -N-tosyllysylglycine. To a solution 2.65 g of the cbz-hexapeptide in 100 ml of methanol was added 0.18 ml of glacial acetic acid and the mixture hydrogenated in the presence of palladium black. The free hexapeptide formed precipitated. After the hydrogenation the suspension was diluted with boiling water, the catalyst removed by filtration, and the solution evaporated to dryness in vacuum. The residue was treated several times with anhydrous ethanol and acetone. The foamy mass obtained was treated again with alcohol and the precipitate collected. We isolated 1.75 g (77.1%) of a substance with m.p. 195-200° (decomp.). The melting point did not change after the hexapeptide had been reprecipitated from water with ethanol. The substance was electrophoretically and chromatographically homogeneous: R_f 0.55.

Found %: C 50.36, 50.29; H 6.37, 6.33; N 13.40. $C_{34}H_{50}O_{11}N_8S_2$. Calculated %: C 50.37; H 6.17; N 13.82.

Cycloglycyl- ϵ -N-tosyllysylglycylglycyl- ϵ -N-tosyllysylglycine. A) To a solution of 250 mg of the hexapeptide in 25 ml of water were added 225 ml of methanol and 1 ml of ethoxyacetylene. The reaction mixture was stirred for 10 hr at 60-70° and then kept at $\sim 20^\circ$ for ten days. The solvent was removed in vacuum and the residue subjected to preparative electrophoresis on cellulose powder [5]. As a result we isolated 60 mg (24%) of a substance which charred above 350° and was insoluble in most organic solvents. The cyclopeptide was chromatographically homogeneous. It had R_f 0.84 (ascending chromatography in the system 1-butanol: water: acetic acid, 4: 5: 1).

Found %: C 50.77, 50.78; H 6.32, 6.24; N 13.99, 13.91. $C_{34}H_{50}O_{10}N_8S_2 \cdot \frac{1}{2}H_2O$. Calculated %: C 50.94; H 6.12; N 13.98.

Partial hydrolysis. A mixture of 5 mg of cycloglycyl- ϵ -N-tosyllysylglycylglycyl- ϵ -N-tosyllysylglycine and 0.5 ml of 1/15 N LiOH was boiled for 1 hr [10]. The starting hexapeptide was detected in the hydrolyzate by paper electrophoresis.

B) A 500-mg sample of glycyl- ϵ -N-tosyllysylglycylglycyl- ϵ -N-tosyllysylglycine was dissolved in a mixture of 50 ml of water and 450 ml of methanol with heating and stirring. The solution was cooled to $\sim 20^\circ$ and 0.55 ml of ethoxyacetylene added to it. The reaction mixture was left overnight at $\sim 20^\circ$, then stirred at 60-70° for 12 hr, and again left overnight at $\sim 20^\circ$. The solvent was then removed in vacuum and the residue subjected to preparative electrophoresis on cellulose powder to yield 146 mg (29.2%) of cycloglycyl- ϵ -N-tosyllysylglycylglycyl- ϵ -N-tosyllysylglycine.

C) To a solution of 100 mg of the tripeptide glycyl- ϵ -N-tosyllysylglycine in a mixture of 25 ml of water and 70 ml of methanol was added 0.1 ml of ethoxyacetylene and the reaction mixture kept at $\sim 20^\circ$ for ten days. The solvent was then removed in vacuum and the residue subjected to preparative electrophoresis on cellulose powder. We obtained 15 mg (15.8%) of cycloglycyl- ϵ -N-tosyllysylglycylglycyl- ϵ -N-tosyllysylglycine, which was identical in properties with the cyclopeptide described in "A", and 70 mg of a mixture of the starting tripeptide and the corresponding hexapeptide.

SUMMARY

The cyclization of peptides in the presence of ethoxyacetylene was studied. The preparation of cycloglycyl- ϵ -N-tosyllysylglycylglycyl- ϵ -N-tosyllysylglycine was described.

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N-ETHYL-MESO-AMINOACRIDINIUM SALTS AND THEIR CONVERSIONS

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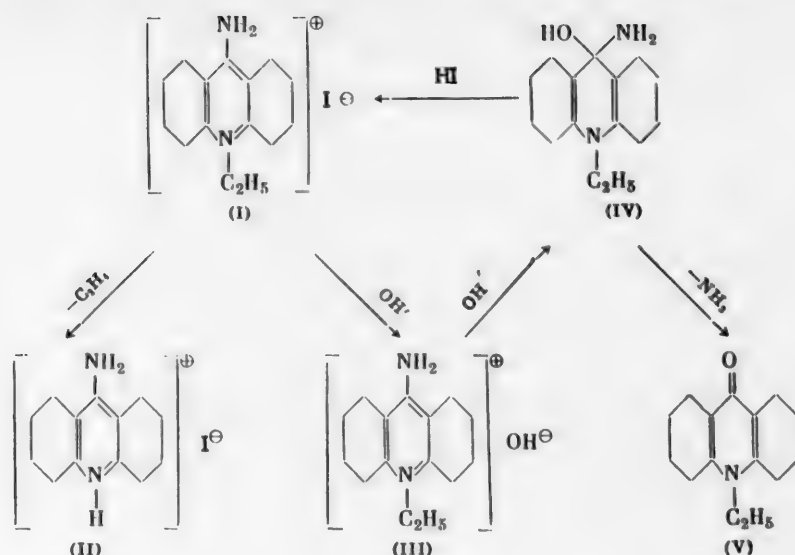
The alkylation products of meso-aminoacridine have not been studied adequately. Only N-methyl-meso-aminoacridinium halides are known [1]. We attempted to prepare other alkyl derivatives by heating meso-aminoacridine with various alkyl iodides. However, it was only in the case of ethyl iodide that we obtained an alkylation product and this was found to be N-ethyl-meso-aminoacridinium iodide (I). The structure of this substance and, in particular, the addition of the ethyl radical to the heterocyclic nitrogen atom was demonstrated by conversion of the substance to N-ethylacridone (V), which was identical with the ethylation product of acridone described by Graebe and Lagodzinski [2]. Contrary to expectations, heating meso-aminoacridine with alkyl iodides containing heavier alkyl radicals such as N-butyl-, N-octyl, and N-cetyl yielded no alkylation products, but the same substance in all cases, and this was found to be the hydroiodide of unsubstituted meso-aminoacridine (II). Assuming that the liberation of this substance was preceded by the formation of the salt of the corresponding N-alkyl derivative, which was unstable under the reaction conditions and decomposed to the salt of unsubstituted aminoacridine with the elimination of an unsaturated hydrocarbon, we decided to check the accuracy of this hypothesis with the N-ethyl derivative (I).

It was found that when heated in alcohol, N-ethyl-meso-aminoacridinium iodide was gradually converted to unsubstituted meso-aminoacridinium iodide (II). This conversion was most complete when the dry salt (I) was heated. By carrying out this decomposition in a stream of carbon dioxide with the volatile reaction products trapped in a burette over potassium hydroxide solution, we obtained an almost quantitative yield of ethylene. From this it follows that when heated in solution and in a dry state, N-alkyl-meso-aminoacridinium salts are unstable and decompose with the elimination of the corresponding olefin and the formation of an aminoacridinium salt which is unsubstituted at the nitrogen. N-Alkyl-meso-aminoacridinium salts containing heavier alkyl radicals are so unstable, probably due to the presence of the latter, that in contrast to the more stable salts of the N-ethyl derivative, they decompose even under the conditions of their formation.

This conversion of N-alkyl-meso-aminoacridinium iodides is noteworthy. The decomposition of quaternary ammonium halides to an alkyl halide and a tertiary amine is more natural. Decomposition with the formation of an unsaturated hydrocarbon is characteristic of quaternary ammonium hydroxides; this is the basis of the classical method of preparing unsaturated hydrocarbons by "exhaustive alkylation" by Willstätter's method [3]. The decomposition of N-alkyl-meso-aminoacridinium iodides described above is probably the result of the distinctive properties of meso-aminoacridine, which, as Albert [1] showed, is a strong base in whose salts the positive charge is distributed through the system of conjugated bonds between the heterocyclic nitrogen atom and the meso-amino group.

The distinctive properties of the meso-aminoacridine grouping also affected the reaction of N-ethyl-meso-aminoacridinium iodide with alkalis. Like cations of basic triphenylmethane dyes, which add a hydroxyl to the central carbon in an alkaline medium and form carbinol bases, the N-ethyl-meso-aminoacridinium cations add a hydroxyl to the meso-carbon to form N-ethyl-meso-amino-meso-hydroxyacridan (IV). This carbinol base, which gradually separated as orange platelets with m. p. 135-138° (with decomp.) when the iodide (I) was treated with potassium hydroxide, was only relatively stable. When heated, it decomposed with the liberation of ammonia and the formation of N-ethylacridone (V).

The behavior of the carbinol base (IV) in the presence of acids is noteworthy. When dilute acids were added to an alcohol solution of the base, the elimination of ammonia with the formation of N-ethylacridone (V) proceeded extremely readily, even without heating. When the dry base was treated with concentrated acids, together with partial conversion to N-ethylacridone, there was salt formation, and the corresponding N-ethyl-meso-aminoacridinium salts were obtained as a result of the liberation of water. Thus, the iodide (I) could be regenerated by treatment of the base (IV) with hydriodic acid, and the chloride and sulfate were obtained by treatment with hydrochloric and sulfuric acids, respectively.



EXPERIMENTAL

N-Ethyl-meso-aminoacridinium iodide. A mixture of 19.4 g (0.1 mole) of aminoacridine and 78 g (0.5 mole) of ethyl iodide was heated under reflux on a boiling water bath for 5 days. The excess ethyl iodide was removed by distillation, and the salt obtained was purified by repeated solution in alcohol and precipitation with ether. The yellow crystals had m.p. 285°.

Found %: N 8.27; I 36.9. $\text{C}_{15}\text{H}_{15}\text{N}_2\text{I}$. Calculated %: N 8.00; I 36.3.

Meso-aminoacridinium iodide. a) Preparation by formation of the salt from the amine. A mixture of 19.4 g (0.1 mole) of aminoacridine and excess 10% hydriodic acid was heated for several hours. The salt obtained was purified by solution in alcohol and precipitation with ether. The yellow crystals had m.p. 312°.

Found %: N 8.72; I 38.9. $\text{C}_{13}\text{H}_{11}\text{N}_2\text{I}$. Calculated %: N 8.7; I 39.5.

b) Preparation by reaction of aminoacridine with alkyl halides. A mixture of 9.7 g (0.05 mole) of aminoacridine with 53.5 g (0.25 mole) of butyl iodide, 61 g (0.25 mole) of octyl iodide, or 95.5 g (0.25 mole) of cetyl iodide was heated under reflux on a boiling water bath for 5 days. After removal of the excess alkyl iodide, the salts obtained were purified by solution in alcohol and precipitation with ether. In all three cases we obtained yellow crystals with m.p. 312°. Mixed melting points with meso-aminoacridinium iodide were not depressed.

c) Decomposition of N-ethyl-meso-aminoacridinium iodide. A 0.35-g sample (0.001 mole) of the substance was decomposed in a vessel under a stream of CO_2 . We collected 20 ml of ethylene (theoretical, 22.4 ml) in a gasometer over 50% KOH solution. The substance remaining in the vessel, which was purified by solution in alcohol and precipitation with ether, was identified as meso-aminoacridinium iodide.

Meso-amino-meso-hydroxy-N-ethylacridan. a) Preparation. A 35-g sample (0.1 mole) of N-ethyl-meso-aminoacridinium iodide was treated with excess 10% KOH at room temperature for several hours. The base obtained was washed free from alkali and purified by repeated solution in alcohol and precipitation with water. The base was obtained as lustrous orange leaflets with m. p. 135-138°.

Found %: N 11.34. $\text{C}_{15}\text{H}_{16}\text{ON}_2$. Calculated %: N 11.65.

b) Decomposition of base in alcohol solution. A 2.4-g sample (0.01 mole) of the base was dissolved in 200 ml of alcohol. Excess 10% hydrochloric acid (or 10% sulfuric acid) was added to the alcohol solution at room temperature. After several hours, the alcohol solution was diluted with water to precipitate cream crystals, which were purified by solution in alcohol and precipitation with water. The product had m.p. 156°. A mixture of the substance obtained and authentic N-ethylacridone melted at 156°.

Found %: N 6.7. $C_{15}H_{13}ON$. Calculated %: N 6.27.

c) Decomposition of dry base. A 2.4-g sample (0.01 mole) of the base was heated to 150° . Ammonia was liberated. After being heated, the substance was dissolved in alcohol and precipitated with water. Cream crystals with m.p. 156° were liberated and these were identified as ethylacridone.

d) Conversion of base to N-ethyl-meso-aminoacridinium salts. N-Ethyl-meso-aminoacridinium chloride. A 2.4 g sample (0.01 mole) of the base was treated with excess 10% hydrochloric acid solution at room temperature for several hours. The salt obtained was washed free from excess acid and purified by repeated solution in alcohol and precipitation with ether. The salt was obtained as yellow crystals with m.p. $295-297^{\circ}$.

Found %: N 10.5; Cl 13.7. $C_{15}H_{15}N_2Cl$. Calculated %: N 10.8; Cl 13.8.

N-Ethyl-meso-aminoacridinium sulfate. A 2.4-g sample (0.01 mole) of the base was treated with excess 10% sulfuric acid at room temperature for several hours. The salt obtained was washed with small portions of water (the salt was appreciably soluble in water) to remove excess acid and purified by recrystallization from water. The salt was obtained as yellow-orange crystals with m.p. $282-285^{\circ}$.

Found %: N 10.4. $C_{20}H_{20}O_4N_4S$. Calculated %: N 10.3.

SUMMARY

1. N-Ethyl-meso-aminoacridinium iodide was formed by the reaction of meso-aminoacridine with ethyl iodide. When heated, it decomposed with the liberation of ethylene and the hydriodide of unsubstituted meso-aminoacridine.
2. When meso-aminoacridine was heated with alkyl iodides containing heavier radicals, only the hydriodide of unsubstituted meso-aminoacridine could be isolated from the reaction mixture, and this indicates the instability of the quaternary salts formed as intermediate products.
3. The action of alkali on an N-ethyl-meso-aminoacridinium salt formed a pseudobase, namely meso-amino-meso-hydroxy-N-ethylacridan, which was converted into N-ethylacridone with the liberation of ammonia when heated in alcohol in the presence of acids. When treated with strong acids, it was converted into N-ethyl-meso-aminoacridinium salts.

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PREPARATION OF HYDROXYLARYL KETONES AND HYDROXYLARYL KETO ACIDS BY ACYLATION OF ALUMINUM PHENOLATES

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One of us showed previously [1] that hydroxyaryl ketones may be obtained by acylation of aluminum phenolates with acid chlorides in the presence of aluminum chloride. The study of this reaction was continued in the present work. Substituted hydroxy ketones were synthesized by acylation of aluminum phenolates with substituted acid chlorides according to the general scheme:



It was also possible to acylate aluminum phenolates with substituents in the nucleus to obtain the corresponding ketones. In the acylation of aluminum phenolates with acid chlorides of dibasic acids, the acid chloride reacted with a molecule of aluminum phenolate to form (after hydrolysis) hydroxyaryl keto acids, for example:



or with two molecules of aluminum phenolate to form a dihydroxy diketone, for example:



Similar hydroxy compounds are obtained differently by the Fries or Friedel-Crafts reaction. Recent investigations [2] showed that (sometimes contrary to previous work) the same products are formed in these reactions, and this makes it necessary to assume that their mechanisms are very similar or even identical. The reaction mechanism in the method proposed is probably analogous. Acylation of aluminum phenolates without the addition of aluminum chloride at the temperature of a water bath yielded the corresponding esters [1] in yields close to theoretical, and therefore it is possible that the synthesis of hydroxyaryl ketones proceeds in two stages: a) formation of the ester and b) a Fries rearrangement. However, the amount of aluminum chloride, even allowing for that formed during the reaction, was no greater and sometimes less (for example, during the synthesis of hydroxybenzophenones) than the equimolecular amount, although the reaction proceeded to completion. The reaction actually proceeded with even smaller amounts of aluminum chloride with heating to 140-160°. However, in these cases the hydroxy ketone obtained always contained some of the corresponding ester, which had to be separated, and we considered this method inconvenient. We should note that in the acylation of aluminum phenolate with p-nitrobenzoyl chloride, we always obtained some ester; part of the aluminum chloride was probably inactivated by the nitro group. In the synthesis of hydroxyacetophenones (including those containing substituents in the benzene ring) by acylation of aluminum phenolate, it was most convenient to carry out the reaction in benzene [1], and the benzene was not acetylated, i.e., acetophenone was not obtained. In the preparation of o- and p-hydroxyacetophenones with a reagent ratio of acetyl chloride: aluminum phenolate = 1: 0.67 (in addition, 0.33 was obtained during the reaction) in benzene, o- and p-hydroxyacetophenones were obtained in good yield (88%) without contamination by phenyl acetate; when twice the amount of aluminum chloride was used and the reaction mixture was heated, 37% of acetophenone and 32% of hydroxyacetophenones were obtained. The Fries rearrangement of phenyl acetate in benzene has been studied in [3]. With a ratio of phenyl acetate to aluminum chloride of 1: 1, a small amount of o- and p-hydroxyacetophenones was obtained, while the ester was largely recovered. With a ratio of 1: 2, up to 60% of acetophenone and a very small amount of p-hydroxyacetophenone were obtained. Comparison shows that these results are quite different, indicating that our reaction may have a different mechanism, for example direct acetylation of aluminum phenolate or diphenoxyaluminum

chloride and phenoxyaluminum dichloride which could be formed during the reaction. The reaction is obviously closer to the Friedel-Crafts reaction than the Fries reaction. The high rate of the reaction we propose may be explained simply by the high activity of the aluminum chloride formed.

On the whole, the reaction described is more convenient than the synthesis of hydroxyaryl ketones by the Fries method as it is not necessary to prepare the ester. This is all the more convenient as esters of some substituted phenols (for example, dichlorophenol) and esters of dibasic acids are often obtained in low yield. As a result, the over-all yield with the reaction described is normally appreciably higher than in the preparation of the same substances by the Fries or Friedel-Crafts method and the consumption of aluminum chloride is less. The ratio of the isomers of the hydroxyaryl ketones obtained is somewhat different, and more of the ortho-isomer is usually obtained than in the Fries or Friedel-Crafts synthesis.

EXPERIMENTAL

In the synthesis of hydroxyaryl ketones that have not been described in the literature, like other investigators, we considered volatility in steam and a color reaction with ferric chloride as indications of an o-hydroxy ketone [4]. The aluminum phenolates were prepared by solution of an equivalent amount of aluminum (turnings) in the appropriate phenol [5] and were used without purification.

Synthesis of hydroxyethylbenzophenones. A mixture of 7.8 g (0.02 mole) of aluminum o-ethylphenolate and 8.4 g (0.06 mole) of benzoyl chloride was heated for 30 min on a water bath. The mixture was cooled, 6.7 g (0.05 mole) of freshly sublimed aluminum chloride added, and the mixture heated for 30 min on a water bath. To the cooled mixture was added 6.7 g (0.05 mole) of freshly sublimed aluminum chloride and the mixture heated on a sand bath at 160-170° for 30 min; hydrogen chloride was liberated. The mixture was cooled, 66 ml of 8% hydrochloric acid added dropwise, and the mixture boiled for 10 min. The 2-hydroxy-3-methylbenzophenone was then distilled with superheated steam. The distilled product was extracted with benzene, dried with magnesium sulfate, and distilled at 165-167° (3 mm). The yield was 8.5 g (61%). The semicarbazone had m.p. 205° (from alcohol).

The residue from steam distillation was dissolved in benzene and extracted 15 times with 3% potassium hydroxide. The combined alkaline extracts were acidified with hydrochloric acid. A precipitate of 4-hydroxy-3-ethylbenzophenone (1.67 g, 12%) had formed after 12 hr. The m.p. was 136° (from alcohol) and the total yield was 73%.

Synthesis of hydroxyethylacetophenones. To a suspension of 7.8 g (0.02 mole) of aluminum tri-o-ethylphenolate in 10 ml of benzene was added 6.7 g (0.05 mole) of freshly sublimed aluminum chloride and 4.7 g (0.06 mole) of acetyl chloride introduced dropwise over a period of 4 hr. After 12 hr, the mixture was heated for 2 hr on a water bath. The mixture was cooled, 40 ml of 8% hydrochloric acid added dropwise at 20-30°, and the mixture then heated to boiling. On cooling, the benzene layer was separated and the aqueous layer extracted twice with 20-ml portions of benzene. The combined benzene solutions were extracted 15 times with 3% potassium hydroxide. The alkaline extract was acidified with hydrochloric acid and the 2-hydroxy-3-ethylacetophenone distilled with superheated steam. The distillate was extracted with benzene, the extract dried with baked magnesium sulfate, the benzene removed, and the residue vacuum distilled. We obtained 3 g (33%) of 2-hydroxy-3-ethylacetophenone with b.p. 90-95° (3 mm). The semicarbazone had m.p. 199° (from alcohol). The residue from steam distillation was filtered hot. We obtained 2.1 g (24%) of 4-hydroxy-3-ethylacetophenone with m.p. 83° (from water), whose p-nitrophenylhydrazone had m.p. 216-217°, which correspond to literature data [6]. The total yield of hydroxyethylacetophenones was 57%. Other hydroxyalkylacetophenones were obtained analogously. The ratios of the reagents and molar amounts were the same. The results are given in the table (Nos. 1-7)*.

For known substances, the constants corresponded to those given in the literature; analyses of new substances are given in the table.

Synthesis of p-nitrohydroxybenzophenones. The reaction was carried out in a three-necked flask with a stirrer, reflux condenser (with a calcium chloride tube), and thermometer. A mixture of 6.2 g (0.02 mole) of aluminum phenolate and 11.2 g (0.06 mole) of p-nitrobenzoyl chloride was heated on a boiling water bath for 30 min. The mixture melted and then partially solidified. The mass was cooled, 6.7 g (0.05 mole) of freshly sublimed aluminum

* T. A. Burtseva helped with this part of the work.

Experi- ment No.	Starting acyl chloride and phenol	Hydroxy ketones obtained	Yield (%)	Boiling point (pressure in mm)	Analysis of compounds and their derivatives
1	Benzoyl chloride and o-ethyl- phenol	2-Hydroxy-3-ethylbenzo- phenone	61	165-167° (3)	Semicarbazone, m.p. 205° (from alcohol). Found %: C 67.95; H 6.11; N 14.89. $C_{15}H_{11}O_2N_3$. Calculated %: C 67.83; H 6.05; N 14.83.
2	Acetyl chloride and o-ethyl- phenol	4-Hydroxy-3-ethylbenzo- phenone (2-Hydroxy-3-ethylaceto- phenone [6]) 4-Hydroxy-3-ethylaceto- phenone [6]	12 33 24	M.p. 136 (from alcohol) 92-96 (3) M.p. 83 (from alcohol)	Found %: C 79.71; H 6.37. $C_{15}H_{13}O_2$. Calculated %: C 79.62; H 6.24. Semicarbazone, m.p. 199° (from alcohol). p-Nitrophenylhydrazone, m.p. 216-217°. Semicarbazone, m.p. 128°.
3	Acetyl chloride and p-ethyl- phenol	6-Hydroxy-3-ethylaceto- phenone [6]	40	100-103 (3)	Semicarbazone, m.p. 197° (from alcohol); oxime, m.p. 119°.
4	Acetyl chloride and o-iso- propylphenol	2-Hydroxy-3-isopropyl- acetophenone 4-Hydroxy-3-isopropyl- acetophenone	50 6	108-110 (3) M.p. 134	Semicarbazone, m.p. 190° (from alcohol). Found %: C 61.46; H 7.41; N 18.01. $C_{13}H_{17}O_2N_3$. Calculated %: C 61.26; H 7.28; N 17.86. Found %: C 74.28; H 8.03. $C_{11}H_{15}O_2$. Calculated %: C 74.13; H 7.92.
5	Acetyl chloride and p-iso- propylphenol	6-Hydroxy-3-isopropyl- acetophenone	53	116-118 (3)	Semicarbazone, m.p. 193° (from aqueous alcohol). Found %: C 61.39; H 7.39; N 18.04. $C_{13}H_{17}O_2N_3$. Calculated %: C 61.26; H 7.28; N 17.86.
6	Acetyl chloride and o-sec- butylphenol	2-Hydroxy-3-sec-butyl- acetophenone 4-Hydroxy-3-sec-butyl- acetophenone	11 8	M.p. 121 M.p. 123	Found %: C 75.10; H 8.52. $C_{13}H_{19}O_2$. Calculated %: C 74.97; H 8.39.
7	Acetyl chloride and p-sec- butylphenol	6-Hydroxy-3-sec-butyl- acetophenone	75	115-119 (3)	Found %: C 75.12; H 8.50; $C_{13}H_{19}O_2$. Calculated %: C 74.97; H 8.39.
8	p-Nitrobenzoyl chloride and phenol	4'-Nitro-2-hydroxybenzo- phenone [8] 4'-Nitro-4-hydroxybenzo- phenone [8] 4'-Nitro-3-methyl-6- hydroxybenzophenone [10]	16 52 52	M.p. 111 M.p. 190 M.p. 142 (from acetone)	Semicarbazone, m.p. 182°. Found %: C 62.83; H 7.82; N 16.98. $C_{13}H_{11}O_5N_3$. Calculated %: C 62.63; H 7.68; N 16.86.

* Condensation temperature 160°. In addition to the ketone, we obtained 3.85 g (25%) of p-tolyl p-nitrobenzoate with m.p. 97°, which corresponds to literature data [11].

Experiment No.	Starting acyl chloride and phenol	Hydroxy ketones obtained	Yield (%)	Boiling point (pressure in mm)	Analysis of compounds and their derivatives
10	p-Bromobenzoyl chloride and phenol	4'-Bromo-2-hydroxybenzo-phenone	23	M.p. 92-92 (from aqueous alcohol)	Found %: C 54.46; H 3.43; Br 28.12. $C_{13}H_9O_2Br$. Calculated %: C 56.34; H 3.27; Br 28.34.
		4'-Bromo-4-hydroxybenzo-phenone	47	M.p. 191 (from aqueous alcohol)	Found %: C 56.57; H 3.54; Br 28.15. $C_{13}H_9O_2Br$. Calculated %: C 56.34; H 3.27; Br 28.34.
11	o-Chlorobenzoyl chloride and phenol	2'-Chloro-2-hydroxybenzo-phenone	32	M.p. 92	Found %: C 67.5; H 4.15; Cl 15.11. $C_{13}H_9O_2Cl$. Calculated %: C 67.10; H 3.90; Cl 15.24.
		4-Chloro-2-hydroxybenzo-phenone	56	M.p. 112	Found %: C 67.39; H 4.10; Cl 15.15. $C_{13}H_9O_2Cl$. Calculated %: C 67.10; H 3.20; Cl 15.24.
12	Benzoyl chloride and 2,4-dichlorophenol	3,5-Dichloro-2-hydroxybenzo-phenone	100	M.p. 114-115	Found %: C 58.61; H 3.11; Cl 26.35. $C_{13}H_5O_2Cl_2$. Calculated %: C 58.45; H 3.02; Cl 26.55.

chloride added, and the mixture heated on an oil bath at 140° for 30 min. Hydrogen chloride was liberated vigorously. The mixture was then cooled to 20° and 100 ml of 8% hydrochloric acid gradually added. The reaction mixture was heated on a boiling water bath for 10 min and cooled, the precipitate removed by filtration, and the filtrate extracted three times with 50-ml portions of ether. The ether extracts were combined, the precipitate dissolved in them, and the hydroxy ketones extracted from the ether solution with ten 50-ml portions of 2% sodium hydroxide. The alkaline extract was acidified with hydrochloric acid. The precipitate of p-nitrohydroxybenzophenones was collected, washed with water, and dried; the yield was 10.4 g (71%). The capacity of 4-nitro-4-hydroxybenzophenone, unlike 4'-nitro-2-hydroxybenzophenone, to dissolve in 5% sodium carbonate [7] was used to separate the isomeric hydroxy ketones. The mixture of hydroxy ketones was triturated in a mortar five times with 5% sodium carbonate solution and the mixture filtered each time. The sodium carbonate solution was acidified with hydrochloric acid and the precipitate collected to yield 7.6 g of 4'-nitro-4-hydroxybenzophenone with m.p. 190° (from aqueous acetone); literature data: m.p. 190-192° [8]. The insoluble residue was recrystallized from acetone. We obtained 1 g of 4'-nitro-2-hydroxybenzophenone with m.p. 111°; literature data: m.p. 111-113° [8]. The ether was distilled from the ether extract (after extraction with 2% sodium hydroxide). We obtained 2.4 g (16%) of p-nitrophenyl benzoate with m.p. 129-130° (from alcohol). Literature data: m.p. 129 [9].

Other hydroxy ketones were obtained analogously from 0.01 mole of aluminum phenolate and 0.03 mole of acid chloride. Where only one isomer was formed without contamination by ester, solution in sodium carbonate was not used. The results are given in the table (Nos. 8-12).

Acylation of aluminum p-cresolate with succinyl chloride.

A mixture of 13.9 g (0.04 mole) of aluminum p-cresolate and 9.3 g (0.06 mole) of succinyl chloride was heated in a round-bottomed flask with an air condenser and a calcium chloride tube on a boiling water bath for 30 min. Then 16 g (0.12 mole) of sublimed aluminum chloride was added and the mixture stirred and heated on an oil bath at 120° for 2 hr. The mass was cooled and hydrolyzed with 8% hydrochloric acid with cooling. The precipitate was collected, washed with cold water, and treated with several portions of 2% sodium hydroxide solution. The insoluble product was collected. The alkaline solution was acidified with hydrochloric acid and the precipitate collected and dissolved in 2 N sodium carbonate solution (about 300 ml). The insoluble part was collected and added to the alkali-insoluble product. The sodium carbonate solution was acidified with hydrochloric acid and filtered after 12 hr. We obtained 3.7 g (12.4%) of β -(2-hydroxy-5-methyl)-phenylpropionic acid with m.p. 136°, which corresponds to literature data [12]. The residue which was insoluble in alkali and sodium carbonate was extracted several times with boiling 2% sodium hydroxide by boiling with the solution and subsequent filtration. The alkaline extract was cooled and acidified with hydrochloric acid. The

precipitate of 1,6-di-(2-hydroxy-5-methylphenyl)-butane-1,4-dione was collected, washed with water, and dried. We obtained 12.8 g (71.5%) of product with m.p. 189° (from propanol), which corresponds to literature data [13].

Acylation of aluminum p-cresolate with adipyl chloride. A mixture of 23 g (0.066 mole) of aluminum p-cresolate and 18 g (0.1 mole) of adipyl chloride was heated on a boiling water bath for 30 min. Then 80.1 g (0.6 mole) of sublimed aluminum chloride was added and the mixture heated for 2 hr on an oil bath at 120° and finally at 160°. The cooled mixture was hydrolyzed with 100 ml of 18% hydrochloric acid and the precipitate collected and washed. It was boiled in 1 liter of 2% sodium hydroxide for 1 hr (for hydrolysis of esters present), the mixture cooled, and the precipitate (24 g) collected. The filtrate was acidified with hydrochloric acid. The precipitate was collected and dissolved in 500 ml of 2 N sodium carbonate solution. The insoluble part (2 g) was added to the alkali-insoluble precipitate. The sodium carbonate filtrate was acidified and the precipitate collected and recrystallized from water. We obtained 3 g (10%) of β -(2-hydroxy-5-methyl)-benzoylvaleric acid with m.p. 119.5°.

Found %: C 66.21; H 6.90. $C_{13}H_{16}O_4$. Calculated %: C 66.10; H 6.78.

The alkali-insoluble product was recrystallized from propanol. It had m.p. 163° and corresponded to 1,6-di-(2-hydroxy-5-methylphenyl)-hexane-1,6-dione [12]. The yield was 26 g (80%).

SUMMARY

1. It was shown that hydroxyaryl ketones, dihydroxydiaryl diketones and hydroxyaryl keto acids may be obtained by acylation of aluminum phenolates.

2. Hypotheses were put forward on the mechanism of the reaction occurring.

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XXXII. COLOR PHENOMENA IN ARYLAMIDES OF p-NITRO- α -PHENYL CINNAMIC AND α -(p-NITROPHENYL)-CINNAMIC ACIDS

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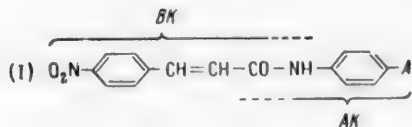
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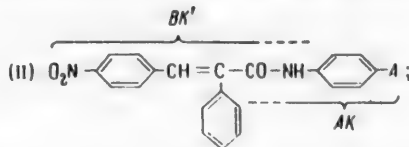
E. A. Smirnov [1] previously studied color phenomena in arylamides of *m*- and *p*-nitro-*trans*-cinnamic acids. All the compounds prepared had a color in the solid state, and the deepest color was shown by derivatives of *p*-nitro-*trans*-cinnamic acid of the general formula (I) with an electron-donor group A [OH, OCH₃, or N(CH₃)₂] in the position para to the NH group.



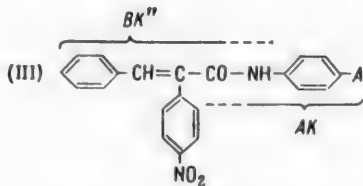
In the opinion of E. A. Smirnov, the main reason for the color of these compounds is a direct interaction through forces of the external field of the two chromophoric systems of opposite nature, namely the electron-donor system AK^* and the electrophilic system BK^{**} , which are separated from each other by a group which stops conjugation ($-CO-NH-$). The presence of color with N-methyl derivatives [with the group $-CO-N(CH_3)-$] indicates that the possible tautomeric conversion of the group $-CO-NH-$ into $-C(OH)=N-$ with the formation of a conjugated chain is not an essential condition for the production of color.

In the present investigation we studied color in analogous arylamides of α -phenyl-substituted trans-cinnamic acids [A represents the same groups as in the derivatives with formula (I)]:

a) derivatives of p-nitro- α -phenylcinnamic acid with the general formula (II):



b) derivatives of α -(p-nitrophenyl)-cinnamic acid with the general formula (III):

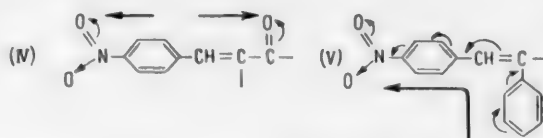


* The electron-donor chromophoric system contains a system of conjugated double bonds with an attached electron-donor group.

- • The electrophilic chromophoric system contains a system of conjugated double bonds with an attached electrophilic group.

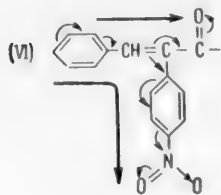
The purpose of the present work was to study the effect of elaboration of the electrophilic chromophoric system (BK' and BK'', respectively, instead of BK), with the electron-donor chromophoric system AK remaining unchanged, on the color of compounds with separated complex chromophoric systems.

This elaboration of the structure of the derivatives of p-nitro- α -phenylcinnamic acid (II) consisted of introducing a benzene ring into the α -position of the molecule of nitrocinnamoyl derivatives (I), which led to considerable lengthening of the π -electron chromophoric system BK. However, in this case the group $-\text{CO}-\text{NH}-$ was not connected to the end of a chain of double bonds, as in the system BK', but to one of the middle units of this chain in the system BK', and the chain itself was thus divided into two parts. One part (the benzene residue) was not conjugated with the CO group and was only subjected to the polarizing effect of an NO_2 group. While molecules of the p-nitrocinnamoyl derivatives (I) contained a strong electrophilic chromophoric system with opposed polarizing effects of the CO and NO_2 groups (IV), in the derivatives of p-nitro- α -phenylcinnamic acid (II), opposed polarization played a lesser role due to the presence of another electrophilic system (V), in which the polarization was in one direction [systems (IV) and (V) are partly superposed on each other].



The structure of the derivatives of α -(p-nitrophenyl)-cinnamic acid (III) differed from that of the p-nitrocinnamoyl derivatives (I) even more appreciably in that not only was there an additional benzene ring in the α -position, but also the nitro group was in this ring and not in the cinnamoyl residue. The molecules of these derivatives did not contain an electrophilic system with opposed polarizing effects, but contained two partially superposed electrophilic systems, at the ends of whose chains were NO_2 and CO groups, respectively (VI) (the directions of the displacement of π -electrons in these systems is indicated by arrows). Since the polarizing effects of these groups on the electrons of the cinnamoyl group compete with each other, this leads to dissipation of the conjugation effect [2], i.e., a decrease in the electronic displacements. Analysis of the structure of these derivatives of phenylcinnamic

acids (II and III) thus leads to the conclusion that due to branching of the chain the electrophilic systems BK' and BK'' in the molecules are weaker chromophoric derivatives (BK). Due to the weakening of the reaction with the electron-donor system AK, a heightening in color is to be expected with a change from arylamides of p-nitrocinnamic acid (I) to the corresponding arylamides of p-nitro- α -phenylcinnamic acid (II) and especially with the change to arylamides of α -(p-nitrophenyl)-cinnamic acid (III).



We prepared arylamides of p-nitro- α -phenylcinnamic acid and α -(p-nitrophenyl)-cinnamic acid which have not been described in the literature (Table 1) and measured both the absorption spectra of the surface of the powders and the

absorption spectra of alcohol solutions of all the substances mentioned above.

The spectroscopic results were compared with data on the spectra of p-nitrocinnamoyl derivatives (I) obtained by E. A. Smirnov and kindly presented to us for the comparison.

Absorption spectra of solutions. The absorption spectra of alcohol solutions we obtained together with those obtained by E. A. Smirnov are shown in Figs. 1 and 2, and data on the absorption maxima of the two bands, namely band I (denoted by λ^I and ϵ^I) and band II (denoted by λ^{II} and ϵ^{II}) are compared in Table 2. For comparison, we also present literature data [3] on the absorption of alcohol solutions of p-nitrostilbene.

As the absorption curves of these substances (Figs. 1 and 2) and the data in Table 2 show, the introduction of an additional benzene ring into the α -position of the nitrocinnamoyl derivatives and, still more, the transfer of the nitro group from the cinnamoyl residue to this ring produce sharp changes in the absorption spectra, which consist not only of displacements of the absorption bands, but also changes in the very nature of the spectrum, namely complete or almost complete disappearance of some bands or steps and their replacement by others, i.e., a change in the form of the absorption curve.

TABLE 1

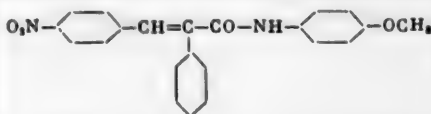
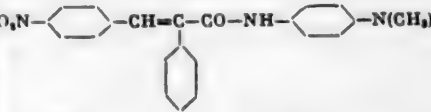
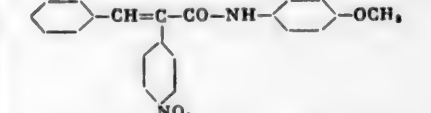
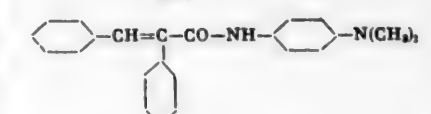
No.	Formula of compound	Color of crystals	Color of powder	Melting point
1		Yellow	Bright yellow	190—190.7°
2		Bright red	Reddish orange	200.5—201.5
3		Yellow	Light yellow	181.5—182
4		Bright red	Yellowish orange	185—186

TABLE 2*

No.	Name	$\lambda_{\text{max}}^{\text{II}}$ m μ	$\epsilon_{\text{max}}^{\text{II}}$	$\lambda_{\text{max}}^{\text{I}}$ m μ	$\epsilon_{\text{max}}^{\text{I}}$
1	p-Nitrocinnamoyl-p-anisidine	300 **	18840 **	~220—230	~12400
2	p-Nitro- α -phenylcinnamoyl-p-anisidine	332 ***	16100 ***	~235—255	~16000
3	α -(p-Nitrophenyl)-cinnamoyl-p-anisidine	278	25500	—	—
4	p-Nitrocinnamoyl-p-amino-dimethylaniline	395	10000	300 ****	27100 ****
5	p-Nitro- α -phenylcinnamoyl-p-aminodimethylaniline	Indistinctly expressed step		304	22700
6	α -(p-Nitrophenyl)-cinnamoyl-p-aminodimethylaniline	~290—310	~20500—22500	267	31800
7	p-Nitrostilbene according to literature data [3]	350	25900	—	—

*~ denotes that λ_{max} and ϵ_{max} were only determined approximately, as the curve had a step.

** In addition there were steps at λ 310–320 m μ ($\epsilon \sim 17600$) and 330–340 m μ ($\epsilon = 16500$).

*** In addition there were steps at λ 310–316 m μ ($\epsilon \sim 15000$) and 322–326 m μ ($\epsilon \sim 15700$).

**** In addition there were steps at λ 250–260 m μ ($\epsilon \sim 12700$).

A comparison of the complex form of the absorption curve (1, Fig. 1) of p-nitrocinnamoyl-p-anisidine with its two band maxima and two steps with the absorption curve of p-nitro- α -phenylcinnamoyl-p-anisidine (2, Fig. 1) shows that on the latter the maximum of band I is displaced toward longer wavelengths by approximately 20 m μ , the maximum at 300 m μ disappears, indistinct steps are present at ~313 and ~324 m μ , and the step at 330–340 m μ

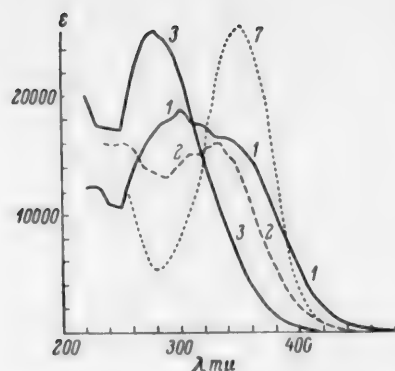


Fig. 1. Absorption spectra of alcohol solutions. 1) p-Nitrocinnamoyl-p-anisidine, 2) p-nitro- α -phenylcinnamoyl-p-anisidine, 3) α -(p-nitrophenyl)-cinnamoyl-p-anisidine, 7) p-nitrostilbene.

(present on curve 1) is converted into the maximum of band II at 332 m μ . However, on the whole the absorption of the whole spectral region above 266 m μ is less intense, while the absorption curve 2 at the edge of the visible part of the spectrum (above 340 m μ) lies parallel to the absorption curve 1 but displaced by approximately 20 m μ toward shorter wavelengths.

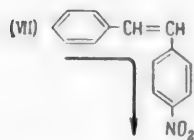
The absorption curve of α -(p-nitrophenyl)-cinnamoyl-p-anisidine (3, Fig. 1) has a completely different, simpler form: The curve has only one band (II) with a maximum displaced toward shorter wavelengths by 22 m μ , but with an increased absorption coefficient (from 18840 to 25500), while there are no steps on the curve at all. The branch of the absorption curve descending toward the visible part of the spectrum (above 310 m μ) lies parallel to that of the nitrocinnamoyl derivative with a hypsochromic displacement of approximately 50 m μ .

Similar phenomena were observed with the spectra of p-amino-dimethylaniline derivatives (Fig. 2). The most complex form, namely two clearly expressed absorption maxima and one step, was shown by the absorption curve of the p-nitrocinnamoyl derivative, which extended far (up to 670 m μ) into the visible part of the spectrum (4, Fig. 2).

A comparison of this curve with the absorption curve of the p-nitro- α -phenylcinnamoyl derivative (5, Fig. 2) shows that the latter lacks the step at 250-260 m μ ; the maximum of band I is not displaced, but its absorption coefficient is somewhat reduced; and then the descending branches of the two curves almost coincide. However, instead of the main band II there is only a quite indistinctly expressed step, so that as a result there is a considerable hypsochromic displacement of the curve in the visible part of the spectrum, and the absorption limit is also displaced to about 580 m μ .

In the absorption spectrum of the α -(p-nitrophenyl)-cinnamoyl derivative (6, Fig. 2) there is a hypsochromic displacement of the maximum of band I by 33 m μ with an increase in the absorption coefficient from 27100 to 31800 and conversion of band II to a step with a hypsochromic displacement of about 90-100 m μ . Above 360 m μ the absorption curve is almost parallel to the curve of the nitrocinnamoyl derivative with a hypsochromic displacement of 70-80 m μ .

The effect of branching of the chain and the presence of two competing electrophilic systems [see above (VI)] on the color is also shown by a comparison of the absorption curves 3 and 6 for α -(p-nitrophenyl)-cinnamoyl derivatives with the absorption curve 7 (in Figs. 1 and 2) for an alcohol solution of p-nitrostilbene, whose molecule contains only one of these systems (VII). Curve 3 for the derivative with a OCH_3 group is displaced hypsochromically over the whole spectral region in comparison with curve 7 and λ_{max} of band II is displaced by 72 m μ . With a stronger electron-donor system AK [with $\text{A} = \text{N}(\text{CH}_3)_2$] curve 6 is also displaced hypsochromically in the ultraviolet region in comparison with curve 7 and λ_{max} of band II is displaced by $\sim 50 \text{ m}\mu$, but curve 6, which intersects curve 7, extends much further into the visible part of the spectrum: The absorption limit lies at $\sim 500 \text{ m}\mu$ and is displaced bathochromically by $\sim 80 \text{ m}\mu$. This can only be explained by the presence of an intramolecular [through the group $-\text{C}(\text{OH}) = \text{N}-$] and probably also an intermolecular interaction of the systems AK and BK⁺ which does not appear so appreciably in a derivative with a weaker electron-donor system (with $\text{A} = \text{OCH}_3$).



Thus, to sum up the results of comparing the absorption spectra, there is a decrease in absorption in the visible and adjacent ultraviolet part of the spectrum due to a hypsochromic displacement of the absorption curve when an additional benzene ring is introduced into arylamides of p-nitrocinnamic acid. Similar but much more considerable changes in the spectrum are observed when the nitro group is transferred into this additional benzene ring, and this completely confirms our theoretical predictions.

Absorption spectra of surface of solid powders. Analysis of the absorption spectra of the surface of the solids generally confirmed the conclusions drawn from the examination of the absorption spectra of alcohol solutions, but the nature of the electron-donor group A had an even stronger effect in the solid state. For compounds containing the OCH_3 group, the absorption curve of the p-nitrocinnamoyl derivatives (1, Fig. 3) lies above the absorption curves

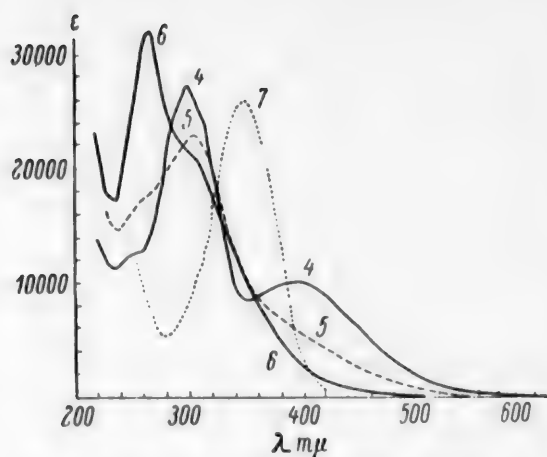


Fig. 2. Absorption spectra of alcohol solutions. 4) p-Nitrocinnamoyl-p-aminodimethylaniline, 5) p-nitro- α -phenylcinnamoyl-p-aminodimethylaniline, 6) α -(p-nitrophenyl)-cinnamoyl-p-aminodimethylaniline, 7) p-nitrostilbene.

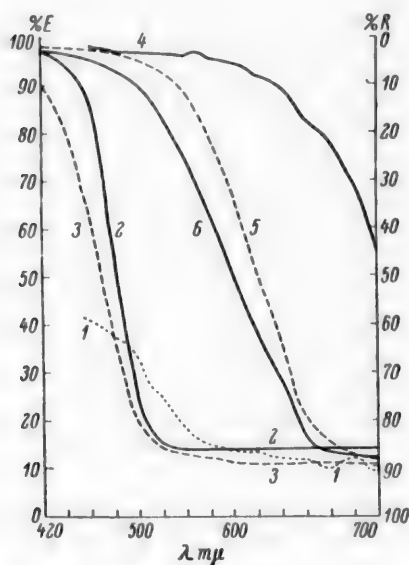


Fig. 3. Absorption spectra of powder surfaces. 1) p-Nitrocinnamoyl-p-anisidine, 2) p-nitro- α -phenylcinnamoyl-p-anisidine, 3) α -(p-nitrophenyl)-cinnamoyl-p-anisidine, 4) p-nitrocinnamoyl-p-aminodimethylaniline, 5) p-nitro- α -phenylcinnamoyl-p-aminodimethylaniline, 6) α -(p-nitrophenyl)-cinnamoyl-p-aminodimethylaniline.

2 and 3 of the phenyl derivatives in only a comparatively narrow section of the spectrum (from 490 to 580 mμ), and in the long-wave region it merges with them or lies just below them*. On the other hand, with compounds containing the $N(CH_3)_2$ group, there is a large difference in absorption over a considerable region of the spectrum; there is a strong hypsochromic displacement of curves 5 and 6 of the phenyl derivatives in comparison with the curve of the p-nitro-cinnamoyl derivative (4).

It should be noted that both with compounds with OCH_3 groups and with compounds with $N(CH_3)_2$ groups, transfer of the NO_2 group to the additional benzene ring produced approximately the same hypsochromic displacement of the absorption curve over the whole of the spectral region examined.

EXPERIMENTAL

A. Derivatives of p-Nitro- α -phenyl-trans-cinnamic Acid**

1. p-Nitro- α -phenyl-trans-cinnamic acid. This substance and the method of preparing it have been described by M. Bakunin [4]. We prepared it in the following way. A mixture of 16.8 g of p-nitrobenzaldehyde, 17.4 g of sodium phenylacetate which had been dried at 130° (1 mole to 1 mole of aldehyde), and 62 ml of acetic anhydride (6 moles to 1 mole of aldehyde) was heated for 6 hr on an oil bath at 160° while a stream of dry carbon dioxide was passed. The cooled reaction mixture was diluted with 80 ml of water and heated to boiling. The mixture was then cooled and the precipitate collected. Recrystallization from alcohol yielded 13.5 g (45.5%) of a pale yellow substance with m.p. 204-212.5°***. Recrystallization from the same solvent did not improve the melting point appreciably (10.65 g, m.p. 206-213°). Fractional crystallization from alcohol yielded 7.5 g of pale yellow crystals with m.p. 213.5-215.5° (literature data: m.p. 213-214° [4] and 217° [5]).

The acid chloride of the above acid was prepared by alternate introduction of acid and an equimolecular amount of phosphorus pentachloride to gently heated phosphorus oxychloride. After removal of the phosphorus oxychloride in vacuum, the acid chloride, which remained as yellow crystals, was dissolved in toluene and this solution used for reactions with amines.

2. N-(p-Nitro- α -phenyl-trans-cinnamoyl)-p-anisidine. A solution of 2.3 g of p-anisidine in 50 ml of water and 1.5 ml of 37% hydrochloric acid was prepared. A toluene solution of the acid chloride obtained from 5 g of p-nitro- α -phenyl-trans-cinnamic acid and then 4 g of sodium bicarbonate were added. After prolonged shaking of the reaction mixture, the precipitate was collected and then

*On visual comparison, the color of powdered p-nitrocinnamoyl-p-aminodimethylaniline (light yellow) seemed even higher than that of the phenyl derivatives (bright yellow).

**The student L. G. Sergeeva helped with the preparation of these derivatives.

***All the melting points given are corrected.

mixed first with 1% hydrochloric acid solution and then, after filtration from this solution, with 1% ammonia solution. We obtained 4.5 g (65%) of product. Recrystallization from alcohol (with the addition of charcoal) and two recrystallizations from acetone yielded yellow needles with m.p. 190-190.7°. The substance was sparingly soluble in alcohol, quite sparingly soluble in benzene and acetone, and readily soluble in chloroform.

Found %: N 7.63. $C_{21}H_{19}O_4N_3$. Calculated %: N 7.48.

3. N-(p-Nitro- α -phenyl-trans-cinnamoyl)-p-aminodimethylaniline. To a solution of 2.55 g of p-amino-dimethylaniline in 5 ml of toluene were added a toluene solution of the acid chloride obtained from 5 g of p-nitro- α -phenyl-trans-cinnamic acid and a solution of 5 g of sodium bicarbonate in water. After prolonged shaking of the reaction mixture, the precipitate was collected (5.2 g, 72%) and recrystallized from benzene and then twice from acetone. Bright red needles with m.p. 200.5-201.5° were obtained.

The substance was difficultly soluble in alcohol and quite difficultly soluble in benzene and acetone. When stirred with 10% hydrochloric acid, the red precipitate changed to a colorless substance, which became red again on treatment with water. The color of the substance did not change in 5% hydrochloric acid.

Found %: N 10.77. $C_{23}H_{21}O_3N_3$. Calculated %: N 10.85.

B. Derivatives of α -(p-Nitrophenyl)-trans-cinnamic Acid

4. α -(p-Nitrophenyl)-trans-cinnamic acid. We prepared this substance according to literature directions [6], but with slight modifications. A mixture of 20 g of p-nitrophenylacetic acid, 7.05 g of benzaldehyde (1.2 mole to 1 mole of acid), 7 g of anhydrous sodium acetate (1.55 mole to 1 mole of acid), and 32 ml of acetic anhydride (6.2 moles to 1 mole of acid) was heated on an oil bath for 12 hr at 170° with a stream of dry carbon dioxide passed. The reaction mixture was then poured into 200 ml of water. When the oil liberated had recrystallized, the precipitate was collected and dissolved in 500 ml of hot water with sodium carbonate added to an alkaline reaction to litmus. After the considerable amount of tar formed had been removed, the filtrate was acidified with hydrochloric acid and the precipitate collected and dried (19.6 g, 66%, m.p. 195-217°). Recrystallization from alcohol with charcoal added gave 11 g (37%) of almost colorless needles with m.p. 227.5-229° (capillary introduced into the bath at 210° and melting point reached after 15 min). Literature data: m.p. 224.5° [7] and 228° [8].

The acid chloride of the above acid was prepared by adding it with an equimolecular amount of phosphorus pentachloride to heated phosphorus oxychloride. There was considerable tar formation during the removal of the phosphorus oxychloride in vacuum, and the residue consisted of a viscous red mass, which was extracted with boiling ligroin (b.p. 80-95°). From the filtrate we isolated light orange crystals of the acid chloride (m.p. ~105-115°), which were used for reactions with amines after drying in a vacuum desiccator. The yield was 40-50%.

5. N-[α -(p-Nitrophenyl)-trans-cinnamoyl]-p-anisidine. To a solution of 1.0 g of p-anisidine in 5 ml of benzene was added a solution of 2.3 g of the acid chloride of α -(p-nitrophenyl)-trans-cinnamic acid in 20 ml of benzene and then a solution 1.5 g of sodium bicarbonate in 20 ml of water. After the reaction mixture had been shaken for 30 min, the yellow precipitate was collected (2.38 g, 78%) and recrystallized from acetone diluted with water, then from benzene, and finally from alcohol. The yellow needles had m.p. 181.5-182°. The substance was quite difficultly soluble in alcohol, more readily soluble in benzene, and readily soluble in acetone.

Found %: N 7.60. $C_{22}H_{19}O_4N_2$. Calculated %: N 7.48.

6. N-[α -(p-Nitrophenyl)-trans-cinnamoyl]-p-aminodimethylaniline. This substance was obtained analogously to the previous one from 0.85 g of p-aminodimethylaniline and 1.8 g of the acid chloride. The orange precipitate which separated (1.51 g, 63%) was collected and recrystallized twice from alcohol. The bright red needles had m.p. 185-186.0°. The substance was quite difficultly soluble in alcohol and readily soluble in benzene and acetone.

Found %: N 11.13. $C_{23}H_{21}O_3N_3$. Calculated %: N 10.85.

Measurement of the absorption spectra of solutions and the absorption spectra of the surface of powdered solids. The absorption spectra of solutions was measured on a Beckmann photoelectric spectrophotometer. The measurements were made with alcohol solutions with concentrations of 10^{-4} M.

For measurement of the reflection spectra, finely ground powder of the substance was rubbed on to semiwhatman* paper and the amount of monochromatic light of various wavelengths reflected from the powder surface compared with the amount of light reflected from magnesium oxide (which was taken as 100%) by means of a photocell. The

* Term not verified - Publisher.

percentage of reflected light found (%R) for all wavelengths was used to find the percentage of light absorbed by the surface (%E) and then the absorption curve of the powdered surface constructed with %E plotted along the ordinate axis, as was recently proposed by V. A. Izmail'skii and V. E. Limanov [9].

The author is very grateful to V. A. Izmail'skii for continuous interest in the work and E. A. Smirnov for providing spectroscopic data.

SUMMARY

1. For studying the effect of elaboration of the structure of the electrophilic chromophoric system BK (with the electron-donor system AK remaining unchanged) in p-nitrocinnamoyl arylamides on the color, we prepared arylamides of p-nitro- α -phenylcinnamic and α -(p-nitrophenyl)-cinnamic acids, where A = OCH₃, N(CH₃)₂ in the position para to the -CO-NH groups.

2. The absorption spectra of alcohol solutions and the absorption spectra of the surface of the powdered substances were measured. These spectra were compared with the spectra of the corresponding p-nitrocinnamoyl derivatives.

3. It was established that the introduction of an additional benzene ring into the α -position of p-nitrocinnamoyl-arylamides produces a hypsochromic displacement of the absorption curve of alcohol solutions in the visible and adjacent ultraviolet parts of the spectrum, with an increase in the absorption at shorter wavelengths.

The transfer of the nitro group to this additional benzene ring produces a further hypsochromic displacement of the absorption curves and also a further increase in the absorption at shorter wavelengths.

4. Analogous phenomena were observed with the absorption spectra of the surface of the solid substances (as powders): There was a hypsochromic displacement of the absorption curve with derivatives with formula (II) and a further hypsochromic displacement with derivatives with formula (III).

5. These phenomena were explained on the basis of an analysis of structural effects on the spectrum.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

SYNTHESIS OF CHELANTS AMONG AZOXY COMPOUNDS

III. NEW SYNTHESIS OF 2-(2-AMINOPHENYLAZOXY)-4-METHYLPHENOL AND MORE

ACCURATE DETERMINATION OF ITS STRUCTURE

V. M. Dzlomko and K. A. Dunaevskaya

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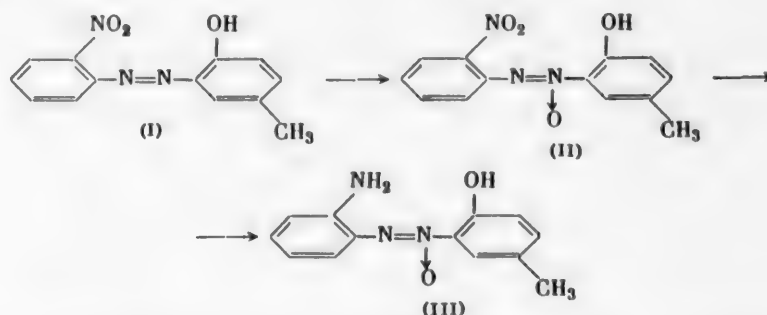
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 1, pp. 68-73,

January, 1961

Original article submitted February 18, 1960

We previously reported [1] the synthesis of 2-amino-2'-hydroxy-5'-methylazoxybenzene (III) by hydrazinolysis of 2-phthaloylamino-2'-hydroxy-5'-methylazoxybenzene. In view of the results of Italian authors [2, 3] on the catalytic reduction of 2-nitrophenylazoxybenzene to 2-aminophenylazoxybenzene, we decided to apply this method to azoxy compounds which could be obtained by oxidation of 2-nitro-2'-hydroxy-5'-methylazobenzene (I).

On oxidation of 2-nitro-2'-hydroxy-5'-methylazobenzene with peracetic acid, we isolated only one azoxy compound. On reduction with hydrogen in the presence of platinum oxide, the latter gave the corresponding amine, which was found to be identical with the amine obtained by hydrazinolysis of 2-phthaloylamino-2'-hydroxy-5'-methylazoxybenzene.

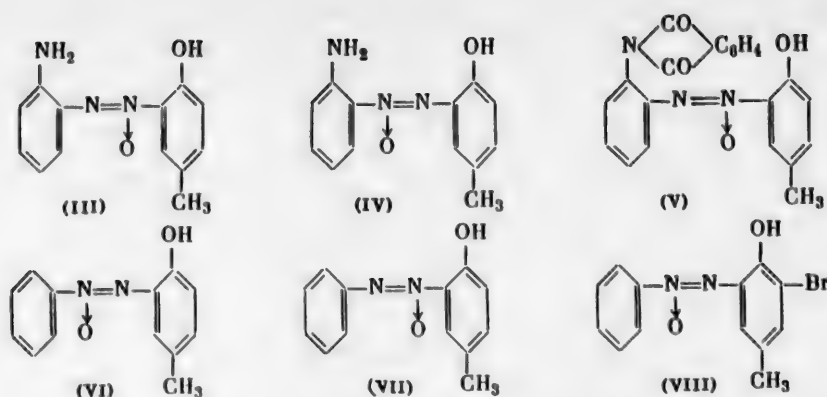


The constancy of the properties of (III) and 2-phthaloylamino-2'-hydroxy-5'-methylazoxybenzene (V) after many purifications and also the results of chromatographic investigations under a wide range of conditions indicated that we had one of the possible isomers of the azoxy compound.

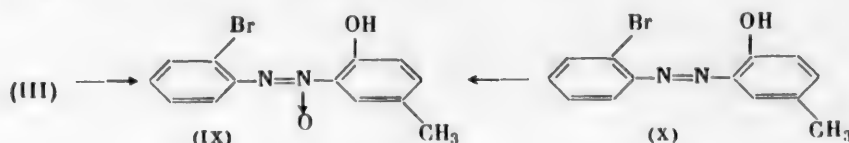
In order to determine the position of the oxygen in the azoxy group more accurately, we brominated under identical conditions 2-phthaloylamino-2'-hydroxy-5'-methylazoxybenzene (V) and the two isomers of benzeneazoxy-p-cresol (VI) and (VII), which have accurately determined structures [4]. It was found that (V) and the β -isomer (VII) were not brominated, while the α -isomer (VI) gave a good yield of 2-hydroxy-3-bromo-5-methylazoxybenzene (VIII).

On the basis of the general property of o-hydroxy azoxy compounds [8] not to undergo substitution under mild conditions in the nucleus containing the hydroxyl group and adjacent to the oxygen of the azoxy group, 2-phthaloylamino-2'-hydroxy-5'-methylazoxybenzene and also 2-amino-2'-hydroxy-5'-methylazoxybenzene must be assigned the structure of β -isomers* (V and III, respectively).

*For denoting α - and β -isomers, the numbering in the azoxy compounds starts from the nucleus without the hydroxyl.



We arrived at the same conclusion on comparing 2-bromo-2'-hydroxy-5'-methylazobenzene (IX) obtained from substance (III) by diazotization and replacement of the diazo group by bromine with 2-bromo-2'-hydroxy-5'-methylazobenzene obtained by oxidation of 2-bromo-2'-hydroxy-5'-methylazobenzene (X). The two products were found to be identical. In addition, they were not brominated under mild conditions by the stoichiometric amount of bromine, which again confirms the accuracy of the structures proposed in which the oxygen of the azoxy group is attached to the nitrogen in the position ortho to the hydroxyl.



Some additional data supporting the structure proposed were obtained by comparing the half-wave potentials* of 2-amino-2'-hydroxy-5'-methylazobenzene (III), 2-phthaloylamino-2'-hydroxy-5'-methylazobenzene (V) and the two isomers of benzeneazoxy-p-cresol (VI and VII), which are given in the table.

Half-Wave Potentials of 2-Amino-2'-hydroxy-5'-methylazobenzene (III), 2-Phthaloylamino-2'-hydroxy-5'-methylazobenzene (V), and the α - (VI) and β - (VII) Isomers of Benzeneazoxy-p-cresol

	Half-wave potential, $E_{1/2}$ (v)
2-Amino-2'-hydroxy-5'-methylazobenzene (III)	0.848
2-Phthaloyl-2'-hydroxy-5'-methylazobenzene (V)	0.802
β -Isomer of benzeneazoxy-p-cresol (VII)	0.832
α -Isomer of benzeneazoxy-p-cresol (VI)	0.938

As the data in the table show, the half-wave potentials of the compounds we synthesized were closer to those of the β -isomer.

For unsymmetrical azoxy compounds, it seems advantageous to us to use the nomenclature proposed by Brough, Lythgoe, and Waterhouse [5]. For example, according to this nomenclature the β -isomer of 2-amino-2'-hydroxy-5'-methylazobenzene should be called 2-(2-aminophenylazoxy)-4-methylphenol.

EXPERIMENTAL

2-Nitro-2'-hydroxy-5'-methylazobenzene (I) was synthesized by diazotization of o-nitroaniline and coupling with p-cresol in a sodium carbonate-alcohol medium. The product was purified by recipitation with ligroin from chloroform solution. It had m.p. 108-110°. Literature data [6]: m.p. 107-108°

*The polarographic investigation was made by Yu. I. Vainshtein and M. D. Shirokova.

Found %: C 60.61, 60.68; H 4.42, 4.47. $C_{13}H_{11}O_3N_3$. Calculated %: C 60.7; H 4.2.

2-(2-Nitrophenylazoxy)-4-methylphenol (II). To a solution of 3.2 g (0.012 mole) of 2-nitro-2'-hydroxy-5'-methylazobenzene in 150 ml of glacial acetic acid was added 40 ml (0.35 mole) of 30% hydrogen peroxide and the mixture heated at 75° for 18 hr. The color of the solution gradually changed from dark red to orange. After filtration, the solution was poured onto 400 g of ice. The product liberated was washed with distilled water on a filter until the filtrate no longer had an acid reaction to Congo Red, dried on the filter, dissolved in 100 ml of methanol, precipitated with 30 ml of water, and dried in a vacuum desiccator over calcium chloride and phosphorus pentoxide. We obtained 1.0 g (30%) of product, which consisted of a yellow powder with m.p. 102-103°. It was readily soluble in methanol, ethanol, chloroform, benzene, ether, and other organic solvents; it was sparingly soluble in water.

Found %: C 57.01, 57.24; H 4.43, 4.36. $C_{13}H_{11}O_4N_3$. Calculated %: C 57.1; H 4.0.

2-(2-Aminophenylazoxy)-4-methylphenol (III). A suspension of 0.2 g of platinum oxide in 20 ml of diethyl ether was shaken with hydrogen until absorption ceased (20 min). Then a solution of 0.4 g (0.0015 mole) of 2-(2-nitrophenylazoxy)-4-methylphenol in 100 ml of diethyl ether was added to the suspension and shaking with hydrogen at room temperature continued until the absorption of hydrogen ceased (1.5-2 hr). The solution was separated from the catalyst by filtration and saturated with dry hydrogen chloride. The precipitate was washed with ether and dissolved in water and the solution neutralized to pH 7 with sodium bicarbonate. The amine (III) liberated was recrystallized from 30 ml of dilute (1: 2) aqueous alcohol and dried in a vacuum desiccator over calcium chloride and phosphorus pentoxide.

The weight was 0.04 g (11%) and the m.p. 125.5°. The melting point of the amine obtained by hydrazinolysis was 126° [1]. The melting point of a mixture was 125.5°.

Found %: C 63.95, 64.0; H 5.62, 5.69; N 17.5, 17.36. $C_{13}H_{13}O_2N_3$. Calculated %: C 64.19; H 5.35; N 17.28.

Bromination of α -benzeneazoxy-p-cresol (VI). To a solution of 0.4 g (0.00175 mole) of α -benzeneazoxy-p-cresol [4] in 10 ml of chloroform was added 0.28 g (0.00175 mole) of bromine. The solution was shaken for 20 min and then poured into a Petri dish and evaporated to dryness. The residue was washed with 50 ml of 36% sodium bisulfite solution and then 50 ml of water, dried on a filter, and recrystallized from 150 ml of ligroin. The weight was 0.3 g and the m.p. 145-146°. Literature data [4]: m.p. 144°.

Found %: C 51.23, 51.02; H 3.91, 3.9. $C_{13}H_{11}O_2N_2Br$. Calculated %: C 50.81; H 3.58.

Bromination of β -benzeneazoxy-p-cresol (VII). A 0.4-g sample (0.00175 mole) of β -benzeneazoxy-p-cresol was brominated analogously to the α -isomer. The product after bromination was recrystallized from 45 ml of ethanol. The weight was 0.23 g and the m.p. 123.5°. A mixture with the original (VII) melted at 123.5°.

Found %: C 68.28, 68.37; H 5.65, 5.62. $C_{13}H_{12}O_2N_2$. Calculated %: C 68.4; H 5.26.

Bromination of 2-(2-phthaloylamino-phenylazoxy)-4-methylphenol (V). A 0.4-g sample (0.00106 mole) of 2-phthaloylamino-2'-hydroxy-5'-methylazoxybenzene [1] was brominated analogously to the α -isomer of benzeneazoxy-p-cresol. After bromination, the product was recrystallized from 40 ml of a dioxane-water mixture (3: 1). The weight was 0.1 g and the m.p. 150°. Substance (V) melted at 150°. A mixture with the starting (V) melted at the same temperature.

Found %: C 67.45, 67.35; H 4.07, 4.36. $C_{21}H_{15}O_4N_3$. Calculated %: C 67.56; H 4.02.

2-(2-Bromophenylazoxy)-4-methylphenol (IX) from 2-(2-aminophenylazoxy)-4-methylphenol (III). A 0.8-g sample (0.0033 mole) of 2-(2-aminophenylazoxy)-4-methylphenol was mixed with 62.5 ml of 40% hydrobromic acid; the mixture was cooled to 0-2° and a solution of sodium nitrite [0.25 g (0.0033 mole) in 10 ml of water] added with stirring. The temperature was kept within the range 0-3°.

For the preparation of cuprous bromide, a mixture of 1.1 g of copper sulfate pentahydrate, 0.32 g of copper turnings, 2.4 g of sodium bromide, 0.32 ml of concentrated sulfuric acid, and 16 ml of water was heated under reflux for 4 hr and then ~0.5 g of sodium sulfite added. The solution of the diazonium hydrobromide was added slowly with stirring to the cuprous bromide at 20-25°. The reaction mixture was stirred for 2-3 hr and the precipitate collected, washed with water (~50 ml), and successively recrystallized twice from aqueous (1: 1) acetone (90 and 20 ml) and twice from dilute (1: 1) aqueous alcohol (28 and 16 ml). We obtained 0.03 g (3%) of product with m.p. 95.5-96°. A mixture with 2-(2-bromophenylazoxy)-4-methylphenol obtained by oxidation of the corresponding azo compound melted at 95.5-96°.

Found %: C 51.02, 51.20; H 4.1, 3.9. $C_{13}H_{11}O_2N_2Br$. Calculated %: C 50.81; H 3.58.

2-(2-Bromophenylazoxy)-4-methylphenol (IX) from 2-bromo-2'-hydroxy-5'-methylazobenzene (X). 2-Bromo-2'-hydroxy-5'-methylazobenzene was synthesized according to data in [7] and purified by successive recrystallizations from acetic acid and methanol. It had m.p. 114°. Literature data [7]: m.p. 116°. The melting point of the acetyl derivative was 85-86°. Literature data [7]: m.p. 85°.

To a solution of 1.4 g (0.0049 mole) of 2-bromo-2'-hydroxy-5'-methylazobenzene in 100 ml of glacial acetic acid was added 16.7 ml (0.14 mole) of 30% hydrogen peroxide and the mixture heated at 70-80° for 18 hr.

The oxidation and isolation of the product were analogous to the oxidation of 2-nitro-2'-hydroxy-5'-methylazobenzene (I) (see above). The product isolated was dried on a filter and recrystallized from 40 ml of a mixture of acetone and water (3:1). We obtained 0.2 g (15%) of product with m.p. 96°, which formed yellow scales. It was readily soluble in ethanol, methanol, chloroform, benzene, acetone, and other organic solvents; it was sparingly soluble in water.

Found %: C 51.03, 51.02; H 4.17, 4.07. $C_{13}H_{11}O_2N_2Br$. Calculated %: C 50.81; H 3.58.

Bromination by the method in [8] yielded only the starting (IX). A mixture melted at 96°.

Found %: C 51.02, 51.20; H 4.1, 4.0. $C_{13}H_{11}O_2N_2Br$. Calculated %: C 50.81; H 3.58.

Chromatographic investigation. Descending chromatography on chromatography paper (slow) was used. The following solvents were used for elution: ligroin saturated with 80% methanol, butanol-acetic acid-water (4:1:5), phenol saturated with water, water-trimethylcarbinol azeotrope, isoamyl alcohol-xylene (2:8) saturated with water, xylene-methanol (2:8) saturated with water, heptane saturated with 80% methanol, ethyl acetate-acetic acid-water (4:1:1), and 60% alcohol. Only one spot was found on all chromatograms of substances (III) and (V).

SUMMARY

1. It was established that the 2-phthaloylamino-2'-hydroxy-5'-methylazoxybenzene was the β -isomer.
2. 2-(2-Nitrophenylazoxy)-4-methylphenol, 2-(2-aminophenylazoxy)-4-methylphenol, and 2-(2-bromophenylazoxy)-4-methylphenol were synthesized.

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REACTIONS OF CYANAMIDE WITH HIGHER ALIPHATIC ACIDS

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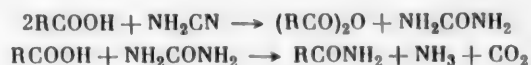
There has recently been a considerable increase in interest in the reactions of cyanamide and dicyanamide with organic compounds [1-4], which offer wide possibilities of the preparation of various nitrogen-containing organic compounds.

The study of the reactions of cyanamide with organic acids, which we discovered, is of great interest. We showed that with the first members of the homologous series, the reaction forms amides and monoureides of the acids. It was established that the yield of the amides increases and the yield of the monoureide decreases with an increase in the molecular weight of the acid.

It was desirable to determine the direction of the reaction between cyanamide and higher aliphatic acids. We used enanthic, pelargonic, lauric, palmitic, and stearic acids for the investigation. Cyanamide and the appropriate acid were taken in a molar ratio of 1:2. A solution of cyanamide in dioxane was added to the acid studied. The reaction mixture was heated for 2.5-3 hr on an asbestos mantle. The main reaction product in all cases was the amide.

According to Rahman [5, 6], urea decomposes at 140° and above in the presence of carboxylic acids to form cyanic acid, which readily isomerizes to isocyanic acid. The latter reacts with carboxylic acids to form an unstable intermediate product, which decomposes to liberate carbon dioxide and form amides.

Considering the complete analytical data on the products of the reactions we investigated and also Rahman's data, the formation of amides from higher aliphatic acids and cyanamide may be represented by the following scheme:



In actual fact, the final reaction products were the amide, ammonia, and carbon dioxide. By combining, the latter formed the ammonium salt of the corresponding acid and also ammonium carbamate, which condensed in the condenser (3%). The cyanic acid polymerized to cyanuric acid, which was sometimes formed in considerable amounts. The absence of an appreciable amount of ureides from the reaction products of cyanamide and higher aliphatic acids may be explained by the decomposition of urea under the reaction conditions in the directions given above and also a fall in the rate of reaction of acid anhydrides with urea as their molecular weight increases.

EXPERIMENTAL

A 20-g sample of enanthic acid was heated to 160° in a three-necked flask with a condenser, dropping funnel, and thermometer. A solution of 3 g of cyanamide in 15 ml of dioxane was added in small portions to the heated acid. When all the cyanamide had been added, the temperature of the reaction mixture was reduced to 145°. The cessation of carbon dioxide liberation at 145-148° indicated the end of the reaction. At the end of the reaction, white crystals of ammonium carbamate had formed on the walls of the reflux condenser and crystals of the amide were deposited on the walls of the reaction vessel. At the end of the heating, the contents of the flask were cooled. The white precipitate which formed during the reaction (1.6 g) was cyanuric acid according to its chemical reactions (formation of melamine cyanurate) and analysis. The dioxane and excess acid were distilled from the filtrate in vacuum. The residue of amide, which solidified on cooling, was recrystallized from methanol.

The amide of pelargonic acid was prepared under the same conditions, except that the reaction temperature was 138-140°. A small amount of the monoureide of pelargonic acid was isolated in addition to the amide.

The amide of lauric acid was obtained at 160-200°. The reaction was carried out with the simultaneous distillation of dioxane. The amide was recrystallized from methanol. For the complete isolation of the amide of lauric acid, water was added to the filtrate from the second recrystallization and white crystals precipitated.

The reactions with palmitic and stearic acids were analogous to that with lauric acid. The experimental data are given in the table.

Sample No.	Substance	Melting point	% N		Amide yield (%)
			found	calculated	
1	Amide of enanthic acid	94-95°	10.6	10.0	77.4
2	Amide of pelargonic acid	98-100	8.6	8.9	43
3	Amide of lauric acid	99-100	7.4	7.02	86.0
4	Amide of palmitic acid	105-106	5.6	5.48	86.7
5	Amide of stearic acid	109-110	4.89	4.93	94.7
6	Monoureide of pelargonic acid	180-186	14.9	14.7	2

SUMMARY

1. The reactions of cyanamide with the higher aliphatic acids enanthic, pelargonic, lauric, palmitic, and stearic acids were studied, and a new method was proposed for the preparation of amides of higher aliphatic acids.
2. A mechanism is proposed for the reaction of cyanamide with higher monobasic unsubstituted aliphatic acids.

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CONVERSIONS OF TRIPHENYLMETHANE DYES IN ACID MEDIA

II. STUDY OF COMPLEX ACID-BASE EQUILIBRIA

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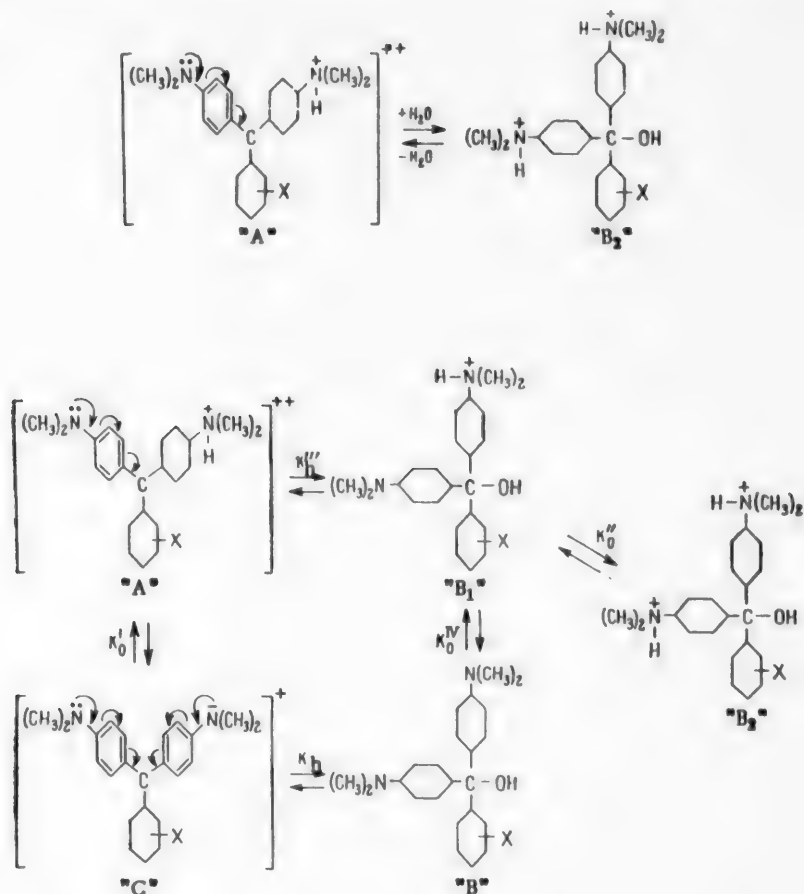
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Doubly charged cations of malachite green and its derivatives which do not contain substituents in a position ortho to the central carbon atom (cations "A") are extremely unstable and undergo further conversions as was reported, in particular, in a previous communication [1]. In recent years papers [2, 3] have appeared in which it was stated that these conversions, which lead to the formation of colorless, doubly charged ammonium ions (cations "B₁"), are connected with the slow addition of a water molecule to the doubly charged cation and this process is reversible. Thus, the slow nature of the formation of colorless compounds from doubly charged cations of malachite green and its derivatives and the formation of the latter from the cations "B₁" are connected with single-stage hydration and dehydration processes.



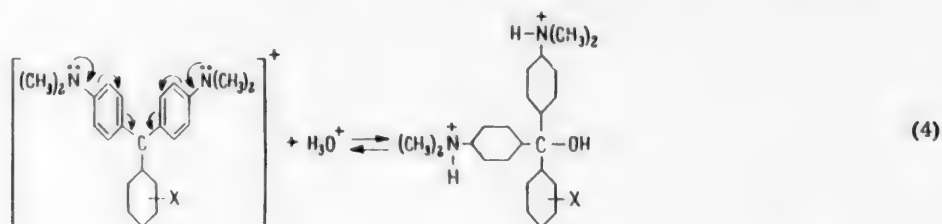
These opinions, with which, however, we cannot agree, are presented in greatest detail by Cigen [4].

Like the singly charged cations "C", the doubly charged cations "A" are conjugated carbonium ions. A characteristic of the doubly charged cations is that they may undergo hydrolysis in two directions, namely, to form ions of the dye "C" and colorless, singly charged cations "B₁"; with the first process occurring instantaneously and the second comparatively slowly. Since, as will be shown below, the basicity constants of the dimethylamino groups in aminotriphenylcarbinols and also in the colorless, singly charged cations "B₁" are hundreds and thousands of times greater than the basicity constants of dimethylamino groups in the singly charged cations (K₀'), under the conditions under which the singly charged cations are converted into the doubly charged cations, the cations "B₁" naturally cannot exist and are immediately converted into the cations "B₂". The conversions given above are shown in scheme 2.

Thus, the conversion of the cation "C" to the cation "B₂" is an example of a three-stage acid-base interaction, with the first and third stages occurring instantaneously and the second comparatively slowly. The process as a whole may be characterized by the composite equilibrium constant K_c, which is the product of the three constants, namely:

$$K_c = \frac{K_w}{K_0'} \cdot \frac{1}{K_h'''} \cdot \frac{K_w}{K_0'} \quad (3)$$

If a solution of malachite green or its derivatives is added to a buffer solution whose pH value equals 0.5-1.0, yellow or yellow-orange solutions are formed first and these are rapidly decolorized. This indicates that at the high pH values given, the acid-base equilibrium in the solutions is practically completely displaced toward the colorless, doubly charged cation "B₂". A different picture is observed if the dye solution is added to a buffer solution with a pH of 2.0-3.0. In this case the buffer solution acquires the bright green color belonging to a mixture of singly and doubly charged cations of the dye. However, this color gradually changes, and the buffer solutions finally acquire the color characteristic of singly charged cations. This shows that in the solution there is actually the equilibrium illustrated by the following scheme:



A quantitative study of the equilibrium (4) made it possible to determine the value of the composite equilibrium constant K_c mentioned above. The values of K_c we found for malachite green and some of its derivatives are given in Table 1.

TABLE 1
Constants Characterizing Equilibria Involving Singly and Doubly Charged Cations of Triphenylmethane Dyes (t = 18 ± 2°)

X	K _c · 10 ³	K ₀ '' · 10 ¹⁰	K _h ''' · 10 ⁴
H	2.3	3.0	2.9
m-OCH ₃	2.0	6.0	1.6
m-Cl	2.0	2.5	7.9
p-Cl	3.2	2.5	4.0

Bodforss and Cigen [2, 4] proposed a series of constants for characterizing the different conversions of triphenylmethane dyes in solution on the basis of very complex arguments with the derivation of more than 60 formulas. Naturally these constants are different from those which we use, as the scheme for the conversions of triphenylmethane dyes developed by Bodforss and Cigen differs from ours. However, as was to be expected, it is possible

to convert the constants calculated by Cigen [4] into the constants given in Table 1. These conversions were carried out for the constants of malachite green, whose reactions were investigated by both Cigen and ourselves.

A comparison of Cigen's data with ours shows, for example, that the constant K_c should correspond to the product of two constants found by Cigen and denoted by him by the symbols K_3 and K_4 . By multiplying the values of the latter for malachite green, we obtained the value $1.8 \cdot 10^{-3}$, which agrees quite satisfactorily with the values of K_c given in Table 1.

As scheme (2) shows, K_c may be characterized not only by Eq. (3), but also by the equation:

$$K_c = \frac{1}{K_h} \cdot \frac{K_w}{K_0^{IV}} \cdot \frac{K_w}{K_0''} \quad (5)$$

A comparison of the structures of the carbinol "B" and the colorless cation "B₁" shows that for the two compounds the basicity constants of the dimethylamino groups should be practically the same ($K_0^{IV} = K_0''$). If we make this assumption, Eq. (5) may be rearranged to the equation

$$K_c = \frac{1}{K_h} \cdot \left(\frac{K_w}{K_0''} \right)^2 \quad (6)$$

By using the values of the hydrolysis constants of the dyes K_h given in Table 2, we calculated the values of K_0'' from Eq. (6) and these are also given in Table 1. As was to be expected, the basicity of the dimethylamino groups in aminotriphenylcarbinols differs little from the basicity of the

TABLE 2

Constants K_h and K_0'' for Dyes of the Malachite Green Group at $t = 18 \pm 2^\circ$

X	$K_h \cdot 10^7$	$K_0'' \cdot 10^{10}$
H	1.2	2.0
m-OCH ₃	1.0	2.0
m-Cl	3.2	1.0
p-Cl	2.0	1.3

dimethylamino group in dimethylaniline itself. Finally, by using the values of K_c and K_0'' and also the values of the basicity constants of the dimethylamino groups in the singly charged cation K_0' which are given in Table 2, from Eq. (3) we calculated the values of K_h'' for the doubly charged conjugated carbonium ions "A", i.e., the constants of the hydrolysis forming the colorless, singly charged cations "B₁". These constants are also given in Table 1. Thus, it was possible to find the constants of all the equilibria given in scheme (2) by calculation.

EXPERIMENTAL

Colorimetric determination of composite constants K_c . To 100 ml of a 10^{-4} molar solution of the carbinol in acetone was added 2 ml of 0.1 N hydrochloric acid solution. On the following day, identical amounts of this acetone solution were added to 25-ml portions of several buffer solutions with various pH values. After equilibrium had been established, the optical densities of the buffer solutions were measured on an SF-4 spectrophotometer at wavelengths of 430 and 620 mμ with a layer thickness of 10 mm. The results of the measurements are given in Table 3. The equilibrium constants were calculated from the equation:

$$pK_c = \text{pH} - \lg \frac{\alpha}{1-\alpha} \quad (7)$$

where $\alpha = \frac{D}{D_{\max}}$, D is the optical density of the solution examined at 620 mμ, and D_{\max} is the optical density of the solution examined at the same wavelength under conditions where the whole of the dye in solution is present as the singly charged cation.

The carbinol compounds were obtained by the action of dilute sodium hydroxide solutions on the corresponding dyes.

The values of the hydrolysis constants of the dyes K_h and the basicity constants of the dimethylamino groups in the singly charged cations of the dyes K_0' , which we found previously or in the present work by the methods described previously [1, 5] and which were required for the calculation of K_0'' and K_h'' , are given in Table 2.

TABLE 3

Change in Optical Density of Dye Solutions in Relation to pH at $t = 18 \pm 1^\circ$

Compound	Amount of dye (ml)	pH	D_{480}	D_{520}	$\frac{D_{520}}{D_{480}}$	α	pK_e
Bis(p-dimethylaminophenyl)phenylcarbinol, m.p. 120-122°	0.2	4.17	0.354	1.50	4.24	1.00	—
		2.8	0.220	0.900	4.08	0.60	2.6
		2.6	0.180	0.748	4.15	0.50	2.6
		2.4	0.138	0.580	4.20	0.39	2.6
Bis(p-dimethylaminophenyl)-m-methoxyphenylcarbinol, m.p. 139-140°	0.1	4.17	0.119	0.560	4.70	1.00	—
		2.6	0.057	0.242	4.45	0.43	2.7
		2.4	0.041	0.188	4.58	0.34	2.7
		2.2	0.030	0.134	4.62	0.24	2.7
Bis(p-dimethylaminophenyl)-m-chlorophenylcarbinol, m.p. 138-141°	0.1	4.21	0.191	0.898	4.70	1.00	—
		2.76	0.110	0.489	4.42	0.54	2.7
		2.43	0.069	0.318	4.65	0.35	2.7
		2.2	0.048	0.216	4.55	0.24	2.7
Bis(p-dimethylaminophenyl)-p-chlorophenylcarbinol, m.p. 146-147°	0.1	4.2	0.129	0.607	4.72	1.00	—
		2.6	0.075	0.338	4.44	0.56	2.5
		2.4	0.058	0.269	4.65	0.44	2.5
		2.2	0.045	0.204	4.55	0.34	2.5

SUMMARY

1. The interconversions of conjugated carbonium ions of triphenylmethane dyes, formed from their carbinol compounds and colorless ammonium ions, are an example of a multistage acid-base interaction.

2. In the equilibrium established in aqueous solutions of malachite green and its derivatives containing substituents in the para- and meta-positions at solution pH values from 0 to 4, the concentration of doubly charged conjugated carbonium ions is extremely low. Therefore, it may be assumed that such solutions contain practically only colorless ammonium ions and singly charged, colored, conjugated carbonium ions.

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SYNTHESIS AND STUDY OF THE CONVERSIONS OF ACETYLENIC α -GLYCOLS

V. REACTION OF 3,4,6-TRIMETHYLHEPT-1-YNE-3,4-DIOL AND 4,5-DIMETHYLHEPT-2-YNE-4,5-DIOL WITH CONCENTRATED SULFURIC ACID AT LOW TEMPERATURE

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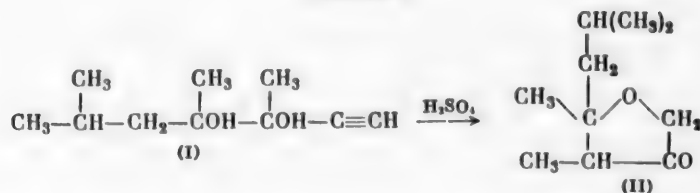
Original article submitted February 29, 1959 [sic]

One of us together with O. A. Zakhar'evskaya [1] studied the reaction of 3,4,6-trimethylhept-1-yne-3,4-diol with dilute sulfuric acid on heating and obtained an enyne alcohol and a dimeric product. By studying the action of concentrated sulfuric acid at -10° on lower homologs of this glycol, namely trimethylacetylenylethylene glycol and 3,4-dimethylhex-1-yne-3,4-diol, we showed [2] that under these conditions the glycols named are converted into substituted tetrahydrofuranones and there is also a pinacol rearrangement to a slight extent.

It seemed interesting to check whether 3,4,6-trimethylhept-1-yne-3,4-diol, which contains the branched isobutyl radical, would undergo an analogous conversion and to determine the effect of replacing the acetylenic hydrogen by a methyl group on the behavior of a glycol we studied previously, namely 3,4-dimethylhex-1-yne-3,4-diol. The conversions of acetylenic α -glycols with various substituted acetylenic radicals have been studied extensively by E. D. Venus-Danilova and her students, but all the glycols they studied contained at least one phenyl group, while the glycol we studied contained only aliphatic radicals; it was therefore interesting to determine whether it would form a hydroxydihydrofuran by the reaction of E. D. Venus-Danilova or give a tetrahydrofuranone like glycols with a free acetylenic hydrogen.

We prepared 3,4,6-trimethylhept-1-yne-3,4-diol (I) in 86% yield by condensation of methylisobutylacetylcarbinol with sodium acetylide in liquid ammonia. The reaction of this glycol with concentrated sulfuric acid at -10 to -15° yielded 2,3-dimethyl-2-isobutyl-4-oxotetrahydrofuran (II) (scheme 1), which gave a 2,4-dinitrophenylhydrazone with m.p. 113° . The structure of this product was demonstrated by plotting the infrared spectrum.

Scheme 1

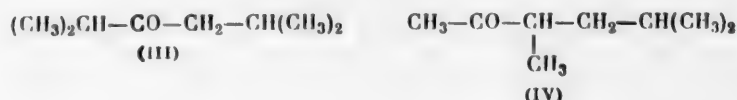


Thus, the reaction of the glycol (I) with sulfuric acid proceeded by the same mechanism as in the case of the other glycols we studied [2]. It is possible that there was another reaction path, namely the formation of the dehydration product and its condensation, as in addition to the furanone (II), in various experiments we obtained from 10 to 30% of a fraction boiling at $70-140^\circ$ (0.5 mm). The substance always resinified during attempts to isolate an individual substance from it by repeated distillation.

The tetrahydrofuranone (II) was found to be much more stable to heating with alkali solution than its simpler homologs; it was unaffected by either 30 or 40% potassium hydroxide solution, and it was decomposed only when boiled with 50% potassium hydroxide solution under reflux for 1.5 hr, and even then half of the furanone was recovered.

The decomposition yielded acetic acid and a ketone, which gave a semicarbazone with m.p. 125-126°, but did not give a crystalline product with 2,4-dinitrophenylhydrazine. Reaction with the latter gave a heavy, thick, dark red oil, whose analysis corresponded to that of the 2,4-dinitrophenylhydrazone of 2,3-dimethyl-2-isobutyl-4-oxotetrahydrofuran.

One might expect decomposition of the tetrahydrofuran (II) to form two ketones, namely isopropyl isobutyl ketone (III) with migration of a methyl radical and 3,5-dimethylhexan-2-one (IV) with migration of the isobutyl radical.



To establish the structure of the ketone we synthesized isopropyl isobutyl ketone, and its constants coincided with those of the keto we obtained; however, the reaction of the ketone (III) with 2,4-dinitrophenylhydrazine gave an orange-yellow crystalline 2,4-dinitrophenylhydrazone and a semicarbazone with m.p. 149-149.5°. The results obtained show that the decomposition of the furanone (II) with alkali yielded the ketone (IV) as a result of migration of the isobutyl radical, as was to be expected since it is known that more complex radicals migrate in preference to simpler ones, but under more drastic conditions than in the decomposition of compounds with simpler radicals [3].

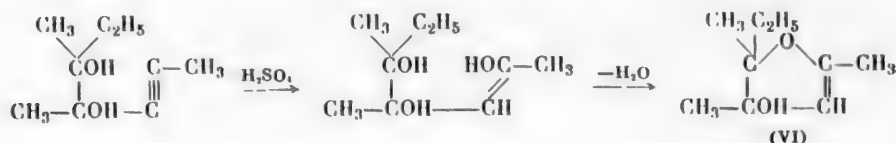
We prepared 3,4-dimethylhept-2-yne-3,4-diol (V) by the reaction of methylethylacetylcarbinol with the sodium derivative of methylacetylene in liquid ammonia. When this glycol was heated with a 10% alkali solution, it decomposed to a keto alcohol and methylacetylene. When hydrogenated over a platinum catalyst, it absorbed 104% of the theoretical amount of hydrogen for a triple bond.

The reaction of glycol (V) with concentrated sulfuric acid at -10° yielded a substance which did not react with 2,4-dinitrophenylhydrazine, give a color with ferric chloride solution, or decompose when boiled with 30% alkali solution. This substance contained one hydroxyl group, and when hydrogenated over a platinum catalyst it absorbed 90% of the theoretical amount of hydrogen for a double bond.

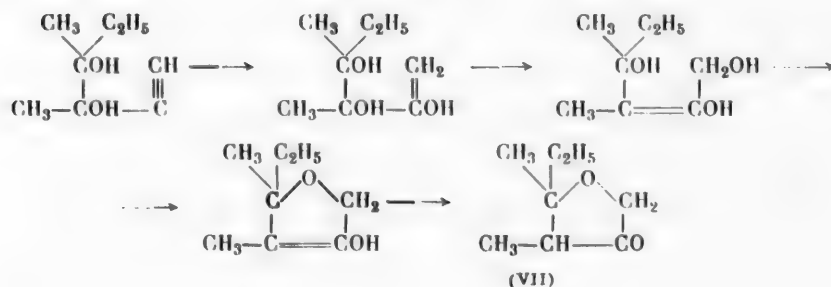
On the basis of these properties, namely the absence of carbonyl and enolic hydroxyl groups and the ease of addition of hydrogen to the double bond, the compound obtained must be assigned the structure of 2,3,5-trimethyl-2-ethyl-3-hydroxy-2,3-dihydrofuran (VI).

The isomerization of the glycol (V) to the hydroxydihydrofuran (VI) may be represented by scheme 2.

Scheme 2



Scheme 3



A comparison of this mechanism with the mechanism of formation of 2,3-dimethyl-2-ethyl-4-oxotetrahydrofuran (VII) (scheme 3) shows that in both cases there is incomplete hydration of the triple bond, but only in the second case is the water molecule added in the reverse order, because there is a methyl group at the triple bond of the glycol (V) instead of hydrogen.

The structure of the hydroxydihydrofuran (VI) was confirmed by oxidation of the compound with potassium permanganate, which gave methyl ethyl ketone and acetic acid.

Thus, though a hydroxydihydrofuran was also obtained in this case, its structure differed from that of the hydroxydihydrofurans obtained by É. D. Venus-Danilova, and consequently the mechanism of its formation differed from that of the latter. It seems to us that this difference may be explained by the different conditions of the reaction of the glycols with sulfuric acid rather than the nature of the radicals present. Heating with dilute sulfuric acid of various concentrations produced a pinacol or acetylene-allene rearrangement with the subsequent formation of hydroxydihydrofurans or there was dehydration. In all probability there was addition of sulfuric acid at the triple bond during the action of concentrated sulfuric acid; the ethylsulfuric acid thus formed was either hydrolyzed or the sulfuric acid was eliminated with the formation of an oxygen bridge.

Depending on the nature of the hydroxyl groups and whether or not the acetylenic hydrogen was replaced, in the case of concentrated sulfuric acid there was the formation of cyclic enols [4], tetrahydrofuranones, or hydroxydihydrofurans.

EXPERIMENTAL

Dimethylisobutylacetylenylethylene Glycol (3,4,5-Trimethylhept-1-yne-3,4-diol) (I) and Its Conversions

Methylisobutylacetylenylcarbinol was obtained both by Favorskii's method and by condensation of methyl isobutyl ketone with sodium acetylide in liquid ammonia. In the first case the yield of the acetylenic alcohol was 70% on the average and in the second case, 50%. The constants of the alcohol obtained agreed with literature data.

Hydration of the acetylenic alcohol by Kucherov's method gave an average yield of methylisobutylacetylenylcarbinol of 50%. The constants of the alcohol corresponded to literature data.

The methylisobutylacetylenylcarbinol was condensed with sodium acetylide in liquid ammonia. The yield of the glycol was 86%.

B.p. 98-99° (8 mm), n_D^{20} 1.4631, d_4^{20} 0.9570, MR_D 48.95. $C_{10}H_{18}O_2$. Calculated 49.35.

Literature data: b.p. 80-83° (3 mm), n_D^{20} 1.4595, d_4^{20} 0.9521.

Reaction of dimethylisobutylacetylenylethylene glycol (I) with sulfuric acid (d 1.84). A 30-g sample of the glycol was added dropwise with cooling to -10° and stirring with a thermometer to 200 ml of sulfuric acid in a 300-ml beaker. The reaction mixture turned brown. After 1.5-2 hr the temperature was raised to room temperature and then the mixture was poured onto 1.5 kg of finely crushed ice. The solution obtained was saturated with ammonium sulfate and extracted with ether, the extract dried, the ether removed, and the residue distilled at 19 mm: 1st fraction, b.p. 57-93°, a few drops; 2nd fraction, b.p. 95-101°, 11 g (35%); 3rd fraction, b.p. 70-140° (0.5 mm), 10 g (30%).

After redistillation, the 2nd fraction had the following constants:

B.p. 99-102° (19 mm), n_D^{20} 1.4529, d_4^{20} 0.9303, MR_D 49.32; calc. 47.84.

Found M 156. $C_{10}H_{18}O_2$. Calculated M 170.

The substance obtained gave a 2,4-dinitrophenylhydrazone with m.p. 113°.

Found %: N 15.93, 15.96. $C_{16}H_{22}O_5N_4$. Calculated %: N 16.00.

The product with b.p. 99-102° (19 mm) obtained decolorized potassium permanganate solution and was oxidized by it. The oxidation of 4 g of the substance consumed 0.5 g of $KMnO_4$. The oxidation product (3 g) had b.p. 98-100° (18 mm), n_D^{20} 1.4529, d_4^{20} 0.9415, MR_D 48.70; calc. 47.84.

Found %: C 70.47, 70.46; H 10.66, 10.74. $C_{10}H_{18}O_2$. Calculated %: C 70.58; H 10.58.

The 2,4-dinitrophenylhydrazone had m.p. 113°; a mixed melting point with the substance obtained previously was not depressed.

Infrared spectrum of 2,3-dimethyl-2-isobutyl-4-oxotetrahydrofuran: NaCl prism, range 850-1720 cm^{-1} . 1704-1710 cm^{-1} - presence of carbonyl group; 1102-1108 cm^{-1} - presence of C-O-C group.

Reaction of 2,3-Dimethyl-2-isobutyltetrahydrofuran-4-one (II) with 50% Potassium Hydroxide Solution

The tetrahydrofuranone obtained was not decomposed by heating with 20 and 40% potassium hydroxide solutions.

A mixture of 30 ml of 50% KOH solution and 3 g of the tetrahydrofuranone was boiled under reflux for 1.5 hr. The cooled mixture was extracted with ether, the extract dried with potassium carbonate, the ether removed, and the residue distilled.

B.p. 45° (10 mm), 143° (atmospheric pressure), n_D^{20} 1.4019, d_4^{20} 0.8111, M_R 39.16; calc. 39.15.

Found %: C 75.10, 74.94; H 12.60, 12.80. M 127. $C_8H_{16}O$. Calculated %: C 75.00; H 12.50. M 128.

The ketone obtained gave a 2,4-dinitrophenylhydrazone as a thick, dark red oil.

Found %: N 17.97, 18.09. $C_{14}H_{20}O_4N_4$. Calculated %: N 18.18.

The semicarbazone from the ketone melted at 125-126°.

The remaining alkaline solution was acidified with sulfuric acid and extracted with ether. The acid remaining after drying and removal of the ether was heated with silver carbonate and the silver salt obtained was analyzed.

Found %: Ag 65.19, 64.76. $C_2H_3O_2Ag$. Calculated %: Ag 64.67.

We prepared isopropyl isobutyl ketone by oxidation of isopropylisobutylcarbinol with chromic acid.

B.p. 147-148° (atmospheric pressure), n_D^{20} 1.4109, d_4^{20} 1.8105.

The 2,4-dinitrophenylhydrazone of the substance was a yellow crystalline precipitate with m.p. 90-91°.

Found %: N 18.07, 17.95. $C_{14}H_{20}O_4N_4$. Calculated %: N 18.18.

The semicarbazone melted at 149-149.5°.

4,5-Dimethylhept-2-yne-4,5-diol (V) and Its Conversions

Methylethylacetylcarbinol was condensed with methylacetylene in liquid ammonia in the presence of metallic sodium. After evaporation of the ammonia, the residue was decomposed with ammonium chloride solution, the reaction product steam distilled, salted out with potassium carbonate, and extracted with ether, the extract dried, the ether removed, and the residue distilled.

We obtained the following fractions:

1st with b.p. 45-50° (3-4 mm) - starting ketol (15 g was recovered out of 73 g); 2nd fraction, b.p. 82-84° (3-4 mm), 24 g (40%).

Investigation of 2nd fraction: B.p. 82-84° (3-4 mm), n_D^{20} 1.4839, d_4^{20} 0.9535, M_R 46.60. $C_9H_{16}O_2F$. Calculated 45.60.

Found %: C 70.34, 70.30; H 10.35, 10.50. Number of H_{act} 1.95, 1.98. M 173. $C_9H_{16}O_2$. Calculated %: C 69.21; H 10.26. Number of H_{act} 2. M 156.

When 0.4074 g of the glycol (V) was hydrogenated in the presence of 0.15 g of platinum black, it absorbed 138 ml of hydrogen, i.e., 104% of the theoretical amount for a triple bond.

Reaction of glycol with alkali solution. A solution of 1 g of glycol in 30 ml of 10% potassium hydroxide solution was distilled slowly and the methylacetylene liberated passed into Ilosvay solution (yellow-green precipitate). The distillate was found to contain methylethylacetylcarbinol, which was identified as the 2,4-dinitrophenylhydrazone.

Reaction of 4,5-dimethylhept-2-yne-4,5-diol with concentrated sulfuric acid. The reaction was carried out under the conditions described above. Distillation of the product obtained yielded 10 g (33%) of a substance.

B.p. 106-110° (17 mm), n_D^{20} 1.4850, d_4^{20} 0.9540, M_R 44.99. $C_9H_{16}O_2F$. Calculated 44.26.

Found %: C 69.29, 69.05; H 10.41, 10.51. Number of H_{act} , 0.79. M 159. $C_9H_{14}O_2$. Calculated %: C 69.21; H 10.24. Number of H_{act} , 1. M 156.

The hydroxydihydrofuran obtained, namely 2,3,5-trimethyl-2-ethyl-3-hydroxy-2,5-dihydrofuran (VI), did not react with 2,4-dinitrophenylhydrazine, give a color with ferric chloride solution, or decompose when boiled with 30% potassium hydroxide solution.

A 1.118-g sample of the hydroxydihydrofuran was hydrogenated in the presence of 0.2 g of platinum black. It absorbed 140 ml of hydrogen, i.e., 90% of the theoretical amount for a double bond.

Oxidation of the hydroxydihydrofuran with potassium permanganate solution yielded methyl ethyl ketone, which gave a 2,4-dinitrophenylhydrazone with m.p. 109°; a mixed melting point with an authentic sample was not depressed. Silver acetate was obtained from the acid products.

Found %: Ag 64.79, 65.03. $C_2H_5O_2Ag$. Calculated %: Ag 64.67.

SUMMARY

1. The reaction of two acetylenic α -glycols, namely 3,4,6-trimethyl-hept-1-yne-3,4-diol and 3,4-dimethyl-hept-2-yne-3,4-diol, with concentrated sulfuric acid at low temperature was studied.

2. It was shown that the first glycol is thus converted into 2,3-dimethyl-3-isobutyl-4-oxotetrahydrofuran, while the second glycol is converted into 2,3,5-trimethyl-2-ethyl-3-hydroxy-2,3-dihydrofuran under these conditions. The hypothesis was put forward that the two conversions proceed by the same mechanism with the intermediate formation of ethylsulfuric acids.

3. 3,4,6-Trimethylhept-1-yne-3,4-diol is decomposed by alkali under more drastic conditions than its homologs with simpler radicals. There is then migration of the isobutyl radical and the formation of 3,5-dimethyl-hexan-2-one and acetic acid. 2,3,5-Trimethyl-3-hydroxy-2,3-dihydrofuran is not decomposed by alkali.

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MECHANISM OF THE DEHYDRATION OF γ -GLYCOLS

VIII. REACTION OF 3-METHYL-1-PHENYLHEX-1-YNE-3,6-DIOL WITH DILUTE SULFURIC ACID

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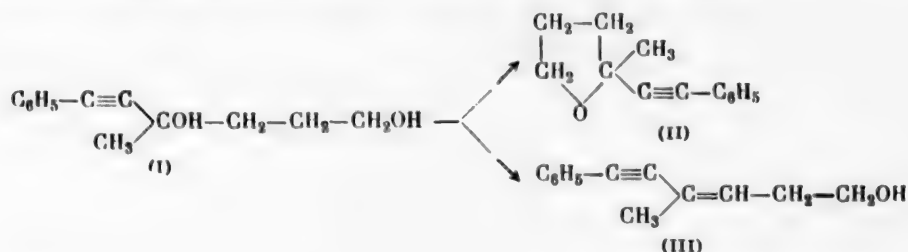
Original article submitted February 29, 1960 [sic]

Together with O. V. Serglevskaya [1] and N. P. Ryzhova [2], we showed previously that primary-tertiary aliphatic γ -glycols are dehydrated under mild conditions to ethylenic glycols, which are isomerized to tetrahydrofuran derivatives by distillation with traces of acid.

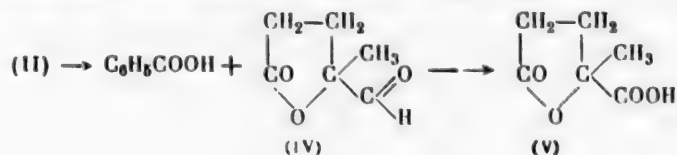
2-Phenylpent-2-en-5-ol and 3-methylhex-2-en-1-yn-6-ol [3] are not isomerized to tetrahydrofuran derivatives; they are stable because of the presence of conjugated multiple bonds. Tetrahydrofurans are formed from the corresponding glycols, namely 2-phenylpentane-2,5-diol and 3-methylhex-1-yne-3,6-diol, by elimination of water at the expense of the two hydroxyl groups.

In the present work we studied the dehydration of the acetylenic γ -glycol 3-methyl-1-phenylhex-1-yne-3,6-diol (I), which was obtained by Iotsich's method from acetopropyl alcohol and phenylacetylenylmagnesium bromide.

Heating this glycol with 5 or 10% sulfuric acid gave a good yield of 2-methyl-2-phenylacetylenyltetrahydrofuran (II). When the glycol was heated with sulfuric acid (pH 1.6) under conditions under which aliphatic glycols yielded ethylenic alcohols, no dehydration occurred and the glycol was recovered. In a repeat synthesis of 3-methyl-1-phenylhex-1-yne-3,6-diol (I), distillation of the reaction products yielded the glycol itself and both its dehydration products, namely the enyne alcohol (III) and the substituted tetrahydrofuran (II). Under some favorable conditions, which were produced by chance, the glycol (I) was dehydrated in both possible ways.

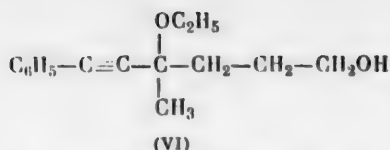


The substance (II) did not react with 2,4-dinitrophenylhydrazine or methylmagnesium iodide and absorbed 2 molecules of hydrogen on hydrogenation. Oxidation of (II) with potassium permanganate solution yielded benzoic acid, 2-methyl-2-formyl-5-oxotetrahydrofuran (IV) and 2-methyl-2-carboxy-5-oxo-tetrahydrofuran (V). Oxidation occurred at the triple bond and with the formation of a lactone grouping.



The structure of the enyne alcohol (III) was demonstrated by hydrogenation and ozonization. During the hydrogenation, 3 molecules of hydrogen were absorbed, and ozonization yielded benzoic, pyruvic, and acrylic acids.

The action of sodium and ethyl bromide in liquid ammonia on the glycol (I) yielded the monoethyl ether of the glycol (VI), namely 3-methyl-1-phenyl-3-ethoxyhex-1-yn-6-ol.



The ethoxyl group was shown to be connected to the third carbon atom of the glycol by heating the ether with alkali solution; decomposition with the formation of phenylacetylene and acetopropyl alcohol did not occur, indicating that there was no free hydroxyl group adjacent to the triple bond.

EXPERIMENTAL

Synthesis of 3-methyl-1-phenylhex-1-yne-3,6-diol (I). The glycol was prepared by the normal method of Iotsich from 50 g of acetopropyl alcohol and 66 g of phenylacetylene and consisted of a thick, colorless liquid with b.p. 166-169° (2 mm). The yield was 42.5%. After several days, the glycol crystallized and had m.p. 46-47°.

B.p. 166-169° (2 mm), n_D^{20} 1.5555, d_4^{20} 1.0619, M_R^D 61.75. $\text{C}_{13}\text{H}_{16}\text{O}_2$. Calculated 60.68.

Found %: C 76.18, 75.98; H 7.70, 8.01. Number of H_{act} , 1.97, 2.00. M 257. $\text{C}_{13}\text{H}_{16}\text{O}_2$. Calculated %: C 76.49; H 7.83. Number of H_{act} , 2. M 204.

When 2 g of the glycol was hydrogenated over 0.2 g of platinum black, 414 ml of hydrogen was absorbed (94.3% of the theoretical amount for a triple bond). The product obtained had n_D^{20} 1.5305.

Reaction of glycol with sulfuric acid. a) A mixture of 10 g of the glycol and 100 ml of 10% sulfuric acid was stirred for 2 hr on a boiling water bath. The reaction products were extracted from the cooled solution with ether and the extract washed with sodium carbonate and water and dried with potassium carbonate. After removal of the ether, the residue was vacuum distilled. We obtained 6.2 g (67.5%) of 2-methyl-2-phenylacetylenyltetrahydrofuran (II).

B.p. 172-175° (45 mm), n_D^{20} 1.5490, d_4^{20} 1.0940, M_R^D 55.90. $\text{C}_{13}\text{H}_{14}\text{O}_2$. Calculated 56.06.

Found %: C 83.76, 83.59; H 7.72, 7.77. M 187. $\text{C}_{13}\text{H}_{14}\text{O}_2$. Calculated %: C 83.86; H 7.53. M 186.

b) A mixture of 4.5 g of the glycol and 45 ml of 5% sulfuric acid was slowly distilled from a Wurtz flask. The acid concentration was kept constant by the continuous addition of water from a dropping funnel. The reaction product distilled at 159-163° (43 mm) and consisted of 2.6 g (63.4%) of tetrahydrofuran (II) with n_D^{20} 1.5492, d_4^{20} 1.0938.

Oxidation of 2-methyl-2-phenylacetylenyltetrahydrofuran (II). The oxidation of 3 g of the tetrahydrofuran consumed 9 g of potassium permanganate. The neutral products were steam distilled. The distillate gave a silver mirror when heated with an ammonia solution of silver oxide and reacted with 2,4-dinitrophenylhydrazine to form a yellow crystalline 2,4-dinitrophenylhydrazone with m.p. 169-170°, which corresponded in composition to that of the aldehyde (IV).

Found %: N 17.38, 17.46. $\text{C}_{12}\text{H}_{12}\text{O}_6\text{N}_4$. Calculated %: N 18.18.

The solution of acid salts was decomposed with sulfuric acid (1:5) and the precipitated benzoic acid (m.p. 120°) collected. A mixed melting point with authentic benzoic acid was not depressed. The acid product was steam distilled from the filtrate and the distillate heated with silver carbonate. We obtained the silver salt of 2-methyl-2-carboxy-5-oxotetrahydrofuran (V).

Found %: Ag 43.09. $\text{C}_6\text{H}_7\text{O}_4\text{Ag}$. Calculated %: Ag 43.03.

On hydrogenation, 2-methyl-2-phenylacetylenyltetrahydrofuran (II) absorbed 112% of the theoretical amount of hydrogen for a triple bond.

Repeat synthesis of 3-methyl-1-phenylhex-1-yne-3,6-diol (I) from 45 g of acetopropyl alcohol and 50 g of phenylacetylene. Vacuum distillation yielded three fractions: 1st, b.p. 132-134° (10 mm), 10 g (8.8%); 2nd, b.p. 165-167° (10 mm), 17 g (19%); 3rd, b.p. 164-165° (2 mm), 18 g (22%).

The 1st fraction corresponded to 2-methyl-2-phenylacetylenyltetrahydrofuran (II). B.p. 132-134° (10 mm), n_D^{20} 1.5470, d_4^{20} 1.0890.

The 2nd fraction was an enyne alcohol, namely 3-methyl-1-phenylhept-3-en-1-yn-6-ol (III).

B.p. 165-167° (10 mm), n_D^{20} 1.5860, d_4^{20} 1.0182, M_R^D 61.53. $C_{13}H_{14}O$ F. F. Calculated 57.69.

Found %: C 82.70, 82.57; H 7.78, 7.96. Number of H_{act} , 0.98, 1.08. $C_{13}H_{14}O$. Calculated %: C 83.86; H 7.53. Number of H_{act} , 1.

The low carbon content may be explained by the presence of some of the 3rd fraction, which consisted of the glycol (I).

A 0.3516-g sample of the enyne alcohol (III) was hydrogenated over Pt black. The amount of hydrogen absorbed was 134 ml (100% of the theoretical amount for a double and triple bond).

Ozonization of 3-methyl-1-phenylhex-3-en-1-yn-6-ol (III). A 2.5-g sample of the alcohol was used for ozonization. The ozonide was decomposed by heating with sodium carbonate solution on a water bath. No neutral products were obtained. The aqueous solution of salts was acidified with dilute sulfuric acid, and the benzoic acid precipitated had m.p. 120° and did not depress the melting point of an authentic sample. The volatile acid was steam distilled from the filtrate and the aqueous solution of it heated with silver carbonate. The silver salt of acrylic acid was obtained.

Found %: Ag 60.30, 60.27. $C_3H_3O_2Ag$. Calculated %: Ag 60.33.

The solution remaining after distillation of the acrylic acid was extracted with ether. The acid remaining after evaporation of the ether gave a 2,4-dinitrophenylhydrazone with m.p. 209-210°. A mixed melting point with authentic pyruvic acid 2,4-dinitrophenylhydrazone was not depressed. When distilled with traces of sulfuric acid, the alcohol (III) was not isomerized to the tetrahydrofuran derivative (II).

Reaction of 3-methyl-1-phenylhex-1-yne-3,6-diol (I) with ethyl bromide and sodium in liquid ammonia. We obtained the ethyl ether of the glycol, namely 3-methyl-1-phenyl-3-ethoxyhex-1-yn-6-ol (VI) as a colorless liquid.

B.p. 182-185° (16 mm), n_D^{20} 1.5225, d_4^{20} 0.9966, M_R^D 71.27. $C_{15}H_{20}O_2$ F. F. Calculated 69.14.

Found %: C 77.97, 77.70; H 8.45, 8.52. Number of H_{act} , 1.076. $C_{15}H_{20}O_2$. Calculated %: C 77.58; H 8.62. Number of H_{act} , 1.

SUMMARY

1. The reaction of the acetylenic γ -glycol 3-methyl-1-phenylhex-1-yne-3,6-diol with dilute sulfuric acid was studied.
2. It was shown that the dehydration of this glycol may proceed in two directions: to form the enyne alcohol 2-methyl-1-phenylhex-3-en-1-yn-6-ol or the substituted tetrahydrofuran 2-methyl-2-phenylacetylenyltetrahydrofuran.
3. 3-Methyl-1-phenylhept-3-en-1-yn-6-ol is not isomerized to 2,2-dimethylphenylacetylenyltetrahydrofuran; the latter was formed by elimination of water from the two hydroxyl groups of the glycol.

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TERTIARY TRIHYDRIC ACETYLENIC ALCOHOLS AND THEIR CONVERSIONS

XXII. DEHYDRATION OF 2-METHYL-5-(1-HYDROXYCYCLOPENTYL)-HEX-3-YNE-2,5-DIOL AND 2,4-DI-(1-HYDROXYCYCLOPENTYL)-BUT-3-YN-2-OL

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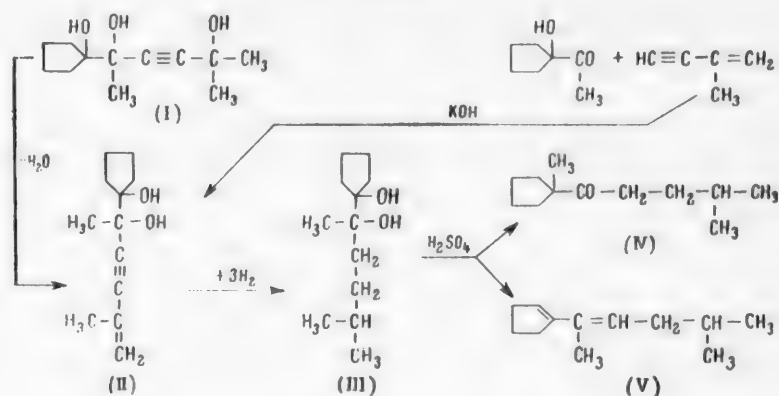
Original article submitted January 23, 1960

The dehydration of various tertiary acetylenic 1,2,5-triols was described in previous communications [1, 2]. It was shown that the triols are dehydrated both with the elimination of one water molecule to form vinylacetylenic α -glycols and with the elimination of two water molecules to form dienynic carbinols. In some cases, the dehydration gives predominantly enynediols and in others, predominantly dienynols, and this apparently depends on the radical substituents in the triol dehydrated.

Below we describe the action of dehydrating agents on two acetylenic triols with one or two cyclopentyl radicals, namely 2-methyl-5-(1-hydroxycyclopentyl)-hex-3-yne-2,5-diol (I) and 2,4-di-(1-hydroxycyclopentyl)-but-3-yn-2-ol (VI), which were synthesized for the first time by one of us and Savranskaya [5].

2-Methyl-5-(1-hydroxycyclopentyl)-hex-3-yne-2,5-diol (I) was treated with *p*-toluenesulfonic acid and potassium bisulfate. In both cases the only dehydration product was a vinylacetylenic glycol, namely 2-methyl-5-(1-hydroxycyclopentyl)-hex-1-en-3-yn-5-ol (II), in a yield of 53 to 59% (scheme 1).

Scheme 1



Hydrogenation of the glycol over both platinum and palladium catalysts in methanol proceeded vigorously. After the addition of 2 moles of hydrogen, the rate of addition of the latter decreased sharply, but it was impossible to isolate the ethylenic glycol by passing in the calculated amount of hydrogen (2 moles) as the reaction products were a difficultly separable mixture.

Exhaustive hydrogenation in both methanol and acetic acid yielded a saturated glycol, namely 2-methyl-5-(1-hydroxycyclopentyl)-hexan-5-ol (III) with m.p. 84-84.5°.

It was impossible to demonstrate the structure of the glycol (II) by oxidation with potassium permanganate because of the complexity of the mixture of oxidation products, and therefore it was demonstrated by the synthesis of

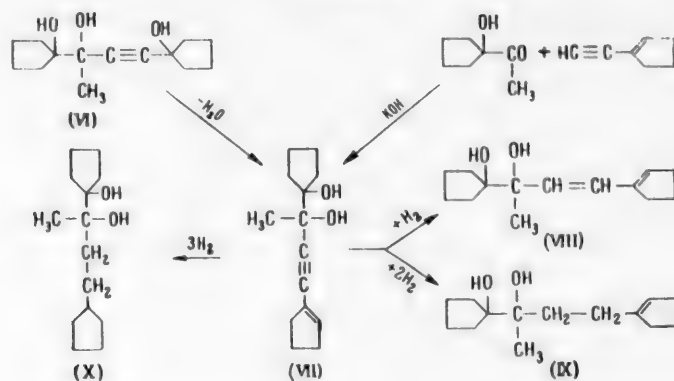
the glycol from isopropenylacetylene and 1-acetylcyclopentanol. The glycol synthesized was hydrogenated to saturation in methanol and the product had m.p. 83.5-84.5°. A mixed melting point with the glycol (III) was not depressed.

When dehydrated with 25% sulfuric acid, the saturated glycol (III) underwent conversion in two directions. Firstly there was a pinacolin rearrangement with the formation of 2-methyl-5-(1-methylcyclopentyl)-pentan-5-one (IV). The ketone itself was not isolated but from the mixture of reaction products we obtained a 2,4-dinitrophenylhydrazone with m.p. 114-116°, whose nitrogen content corresponded to the hydrazone of the given ketone. Secondly, there was dehydration of the glycol with the elimination of 2 water molecules and the formation of a diene compound, which was also not isolated, but we were able to isolate the product from its condensation with maleic anhydride (a crystalline product with m.p. 126-128°) and on this basis the diene was considered to be 2-methyl-5-cyclopenten-1-ylhex-4-ene (V) (scheme 1).

In the dehydration of the glycol (III) with potassium bisulfate there was also a pinacolin rearrangement with the formation of (IV).

As regards the other acetylenic triol, 2,4-di-(1-hydroxycyclopentyl)-but-3-yn-2-ol (VI), it was also dehydrated with p-toluenesulfonic acid and potassium bisulfate. The amount of the latter had to be reduced considerably in this case as otherwise there was very much tar formation. As a result of the dehydration we isolated an enyne α -glycol, namely 2-(1-hydroxycyclopentyl)-4-cyclopentenylbut-3-yn-2-ol (VII), in 28% yield (scheme 2).

Scheme 2



A characteristic of this enyne α -glycol was the fact that it could be hydrogenated selectively by 1 mole of hydrogen to a diene α -glycol, namely 2-(1-hydroxycyclopentyl)-4-cyclopentenylbut-3-en-2-ol (VIII). The latter was characterized by the fact that it underwent diene condensation with maleic anhydride to give a crystalline product with m.p. 276-280°.

Hydrogenation of the glycol (VII) over palladium on chalk (2 moles of hydrogen were passed in) gave an ethylenic glycol, the position of whose double bond we did not establish. However, considering that in all cases of hydrogenation of enyne α -glycols to ethylenic glycols carried out previously in the work given above [1, 2], the triple bond was always saturated, we consider that in this case the ethylenic α -glycol we obtained was 2-(1-hydroxycyclopentyl)-4-cyclopentenylbutan-2-ol (IX).

Exhaustive hydrogenation of 2-(1-hydroxycyclopentyl)-4-cyclopentenylbut-3-yn-2-ol (VII) in methanol yielded the saturated glycol 2-(1-hydroxycyclopentyl)-4-cyclopentylbutan-2-ol (X) with m.p. 81.5-82.5°.

The structure of the glycol (VII) was demonstrated by its synthesis from cyclopentylacetylene and 1-acetylcyclopentanol. The glycol obtained was hydrogenated completely in methanol, and after recrystallization from ligroin the product had m.p. 80-82°. A mixed melting point with the glycol (X) was not depressed (scheme 2).

EXPERIMENTAL

I. 2-Methyl-5-(1-hydroxycyclopentyl)-hex-3-yne-2,5-diol (I)

Dehydration of 2-methyl-5-(1-hydroxycyclopentyl)-hex-3-yne-2,5-diol. 1) With p-toluenesulfonic acid. A 19.3-g sample of the triol (I) with 0.05 g of p-toluenesulfonic acid was distilled at 4.5-5.5 mm and a bath temperature

of 155-160°. We distilled 14.8 g of a substance with b.p. 110-115°. We dehydrated a total of 39.6 g of the triol and obtained 30 g of moist dehydration product, which was dissolved in ether and dried with sodium sulfate. Removal of the ether and vacuum distillation yielded a fraction with b.p. 105-109° (1 mm) and n_D^{20} 1.5152 (23.4 g, 64%, considering that the enyne glycol II was obtained).

2) With potassium bisulfate. A 20.5-g sample of the triol (I) was distilled at 165° and 2 mm in the presence of 10 g of finely ground potassium bisulfate and 0.01 g of hydroquinone. The distillate consisted of 15.6 g of moist product with b.p. 70-124°. Drying and a second vacuum distillation in a stream of carbon dioxide yielded 59% (on the starting material) of 2-methyl-5-(1-hydroxycyclopentyl)-hex-1-en-3-yn-5-ol (II), whose structure was demonstrated by synthesis.

Investigation of 2-methyl-5-(1-hydroxycyclopentyl)-hex-1-en-3-yn-5-ol (II).

B.p. 119-120° (3 mm), d_4^{20} 1.0260, n_D^{20} 1.5152, M_R 57.05, $C_{12}H_{18}O_2$. Calculated 56.00.

Found %: C 74.39, 74.29; H 9.27; OH 16.98, 16.25. $C_{12}H_{18}O_2$. Calculated %: C 74.22; H 9.22; OH 17.53.

A 22.2-g sample of the vinylacetylenic glycol (II) was hydrogenated in 10 ml of methanol over platinum oxide for 4 hr. After the absorption of 6.3 liters of hydrogen (22° and 695.0 mm) the hydrogenation rate was sharply decreased (2 moles of hydrogen corresponds to 6.064 liters). After removal of the methanol, the residue was vacuum distilled, but it was impossible to isolate a homogeneous product. Therefore, 20.5 g of the mixture was hydrogenated further over platinum oxide in 40 ml of glacial acetic acid; 2.8 liters of hydrogen was absorbed in 4 hr and then hydrogenation ceased. The acetic acid was neutralized with sodium carbonate, the hydrogenation product extracted with ether, the extract dried with sodium sulfate, the ether removed, and the residue vacuum distilled. We isolated 17.7 g of 2-methyl-5-(1-hydroxycyclopentyl)-hexan-5-ol (III) with m.p. 84-84.5° (from ligroin).

Found %: C 72.18, 71.71; H 12.11, 12.15; OH 16.18, 16.46. $C_{12}H_{24}O_2$. Calculated %: C 72.00; H 12.00; OH 17.00.

Synthesis of 2-methyl-5-(1-hydroxycyclopentyl)-hex-1-en-3-yn-5-ol (II). Starting materials: isopropenylacetylene, which was prepared according to literature directions [6], boiled at 32-35° (n_D^{20} 1.4120). Acetylcyclopentanol, which was obtained by hydration of acetylenylcyclopentanol [2], boiled at 69-70° (8 mm) (n_D^{20} 1.4665).

A mixture of 17.5 g of isopropenylacetylene and 30 g of acetylcyclopentanol in 100 ml of absolute ether was added dropwise to 50 g of potassium hydroxide and 500 ml of absolute ether over a period of 3.5 hr. On the following day the complex formed was decomposed with 100 ml of water and the ether layer separated from the aqueous alkaline layer, which was extracted several times with ether. The ether layer was neutralized with 5% hydrochloric acid, washed with water, and dried with sodium sulfate. After removal of the ether, the substance was vacuum distilled. We isolated: 1st fraction, b.p. 43-102° (1.5 mm), n_D^{20} 1.4690, 3.2 g, starting acetylcyclopentanol; 2nd fraction, b.p. 102-104° (1.5 mm), n_D^{20} 1.5153, 18.5 g, 2-methyl-5-(hydroxycyclopentyl)-hex-1-en-3-yn-5-ol (II).

Hydrogenation of the enynediol (II) synthesized. A 2-g sample of the enynediol (II) synthesized was hydrogenated in 40 ml of anhydrous methanol over platinum oxide. In 30 min, 0.8 liter of hydrogen (18°, 700 mm) was absorbed (0.74 liter corresponds to 3 moles of hydrogen). After removal of the methanol, the substance melted at 83.5-84.5° (from ligroin). A mixed melting point with 2-methyl-5-(1-hydroxycyclopentyl)-hexan-5-ol (III) was not depressed.

Dehydration of 2-methyl-5-(1-hydroxycyclopentyl)-hexan-5-ol (III). 1) With sulfuric acid. A mixture of 14.9 g of the substance and 160 ml of 25% sulfuric acid was heated for 5 hr on a boiling water bath and then left at room temperature for 4 hr. Isolation of the reaction products in the usual way yielded several fractions, each of which consisted of a mixture of substances (hydroxyl groups were absent); from these fractions it was possible to isolate a substance whose 2,4-dinitrophenylhydrazone had m.p. 114-116° and corresponded in analysis to the 2,4-dinitrophenylhydrazone of the ketone expected, namely 2-methyl-5-(1-methylcyclopentyl)-pentan-5-ol (IV).

Found %: N 15.76. $C_{11}H_{20}O_4N_4$. Calculated %: N 15.46.

In addition, we obtained a substance which gave a diene condensation product with maleic anhydride with m.p. 126-128°, whose diene component was evidently 2-methyl-5-cyclopentenylhex-4-ene (V).

2) With potassium bisulfate. A mixture of 4.4 g of substance (III) and 2 g of finely ground potassium bisulfate was distilled slowly at 3.5 mm and a bath temperature of 140°. Thereupon there distilled 3.2 g of moist product with

b.p. 70-85°. Crystals of the starting glycol with m.p. 82-84° deposited on standing. The filtrate was vacuum distilled, but it was impossible to obtain a homogeneous product. Treatment with 2,4-dinitrophenylhydrazine yielded a 2,4-dinitrophenylhydrazone with m.p. 114-116°, which indicated that the dehydration gave the ketone (IV). A mixed melting point with the phenylhydrazone of the ketone obtained in experiment 1 was not depressed.

II. 2,4-Di-(1-hydroxycyclopentyl)-but-3-yn-2-ol (VI)

Dehydration of 2,4-di-(1-hydroxycyclopentyl)-but-3-yn-2-ol. 1) With p-toluenesulfonic acid. A 9.4-g sample of 2,4-di-(1-hydroxycyclopentyl)-but-3-yn-2-ol (VI) with 0.05 g of p-toluenesulfonic acid was distilled in a stream of carbon dioxide at 3 mm and a bath temperature of 130°. Thereupon there distilled 2.25 g of a very unstable product with b.p. 95-100°. The dehydration was accompanied by considerable tar formation.

2) With potassium bisulfate. A mixture of 5.7 g of the triol (VI) and 0.5 g of finely ground potassium bisulfate was distilled at 180-185° in a stream of carbon dioxide at 4-5 mm. Thereupon there distilled 3.6 g of a substance with b.p. 150-156°, which turned green on standing. It was necessary to use such small amounts of the triol for dehydration as considerable amounts of tar were formed with an increase in the heating time. We dehydrated a total of 11.1 g of the substance and isolated 7.2 g of moist product, which was dried and vacuum distilled twice to yield 2.8 g of 2-(1-hydroxycyclopentyl)-4-cyclopentylbut-3-yn-2-ol (VII).

B.p. 139-141° (2 mm), d_4^{20} 1.0807, n_D^{20} 1.5386, M_R^D 63.77. $C_{14}H_{20}FF$. Calculated 63.03.

Found %: C 76.17, 76.28; H 9.08, 9.04; OH 14.38; 14.09. $C_{14}H_{20}O_2$. Calculated %: C 76.37; H 9.09; OH 15.42.

Hydrogenation of 2-(1-hydroxycyclopentyl)-4-cyclopentenylbut-3-yn-2-ol (VII). 1) To the diene glycol (VIII). A 2.4-g sample of the enyne glycol (VII) in 40 ml of anhydrous methanol was hydrogenated over palladium on chalk. The calculated amount of hydrogen (1 mole, 16.5°, 699 mm), 270 ml, was absorbed in 20 min. Removal of the methanol and vacuum distillation (considerable tar formation) yielded 1.4 g (58%) of 2-(1-hydroxycyclopentyl)-4-(cyclopentenyl)-1-but-3-en-2-ol (VIII).

B.p. 138-140° (3 mm), d_4^{20} 1.0640, n_D^{20} 1.5262, M_R^D 64.77. $C_{14}H_{22}O_2F_2$. Calculated 64.56.

Found %: C 75.67, 75.43; H 9.98, 9.93; OH 13.94, 13.29. $C_{14}H_{22}O_2$. Calculated %: C 75.67; H 9.90; OH 15.32.

A diene condensation product was obtained with maleic anhydride; it had m.p. 276-280°.

2) To the ethylenic glycol (IX). A 4.2-g sample of the enynediol (VII) in 40 ml of anhydrous methanol was hydrogenated over palladium on chalk. The calculated amount of hydrogen (2 moles or 1.03 liter at 27° and 693 mm) was absorbed in 2 hr; hydrogenation was then stopped. Vacuum distillation yielded 2.5 g (59%) of a fraction with b.p. 133-142° (2 mm), n_D^{20} 1.5170, which was vacuum distilled again.

B.p. 133-137° (2 mm), d_4^{20} 1.0420, n_D^{20} 1.5165, M_R^D 64.98. $C_{14}H_{24}O_2F$. Calculated 65.03.

Found %: C 75.60; H 10.65; OH 12.94. $C_{14}H_{24}O_2$. Calculated %: C 75.00; H 10.71; OH 15.75.

According to analysis data, the substance corresponded to 2-(1-hydroxycyclopentyl)-4-(1-cyclopentenyl)-butan-2-ol (IX).

3) Exhaustive hydrogenation to 2-(1-hydroxycyclopentyl)-4-cyclopentylbutan-2-ol (X). A 3.5-g sample of the enynediol (VII) in 40 ml of anhydrous methanol was hydrogenated over platinum oxide. The calculated amount of hydrogen (3 moles or 1.18 liter at 14° and 700 mm) was absorbed in 2 hr. After removal of the methanol, the substance melted at 81.5-82.5° (from ligroin).

Found %: C 74.42, 74.01; H 11.72, 11.76; OH 15.63, 14.71. $C_{14}H_{26}O_2$. Calculated %: C 74.33; H 11.50; OH 15.04.

The product with m.p. 81.5-82.5° was 2-(1-hydroxycyclopentyl)-4-cyclopentylbutan-2-ol (X).

Synthesis of 2-(1-hydroxycyclopentyl)-4-cyclopentylbut-3-yn-2-ol (VII). Starting materials: the cyclopentenylacetylene, which was prepared according to literature directions [4], boiled at 58-62° (n_D^{20} 1.4900). Acetylcyclopentanol was prepared by hydration by Kucherov's method [3] and had b.p. 69-70° (8 mm), n_D^{20} 1.4665.

A mixture of 11.6 g of cyclopentenylacetylene and 12.8 g of acetylcyclopentanol in 100 ml of absolute ether was added dropwise over a period of 1.5 hr to 20 g of potassium hydroxide and 300 ml of ether. After the addition,

the reaction mixture was stirred for a further 6 hr. Isolation of the products in the usual way and two vacuum distillations yielded: 1st fraction with b.p. 55-56° (2 mm), n_D^{20} 1.5300, 2.2 g; 2nd fraction with b.p. 148-149° (2 mm), n_D^{20} 1.5384, 7.2 g, 2-(1-hydroxycyclopentyl)-4-cyclopentenylbut-3-yn-2-ol (VIII).

Hydrogenation of 2-(1-hydroxycyclopentyl)-4-cyclopentenylbut-3-yn-2-ol synthesized. A 2.5-g sample of the glycol (VII) synthesized was hydrogenated in 40 ml of methanol over platinum oxide. The calculated amount of hydrogen (3 moles or 0.88 liter at 16° and 696 mm) was absorbed in 1.5 hr. After removal of the methanol, the substance had m.p. 80-82° (from ligroin). A mixture with the glycol (X) melted at 80.5-82.5°.

SUMMARY

1. Two acetylenic 1,2,5-triols, namely 2-methyl-5-(1-hydroxycyclopentyl)-hex-3-yne-2,5-diol and 2,4-di-(1-hydroxycyclopentyl)-but-3-yn-2-ol were dehydrated. In the two cases the corresponding enyne α -glycols, namely 2-methyl-5-(1-hydroxycyclopentyl)-hex-1-en-3-yn-5-ol and 2-(1-hydroxycyclopentyl)-4-cyclopentenylbut-3-yn-2-ol, respectively, were isolated.

Dienyne carbinols were not isolated.

2. 2-(1-Hydroxycyclopentyl)-4-(cyclopentenyl-1)-but-3-yn-2-ol was hydrogenated selectively over palladium on chalk to the diene glycol 2-(1-hydroxycyclopentyl)-4-(cyclopentenyl-1)-but-3-en-2-ol.

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ALKYLATION OF AROMATIC COMPOUNDS WITH DIENES

I. ALKENYLATION OF ANISOLE WITH PIPERYLENE IN THE PRESENCE OF BORON TRIFLUORIDE ETHYL ETHERATE

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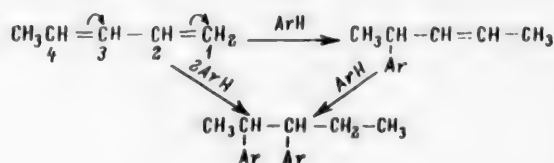
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 1, pp. 95-102,

January, 1961

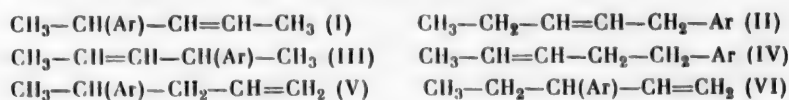
Original article submitted October 27, 1959

Nuclear alkylation of aromatic compounds with dienes has been studied little [1-3]. The process is usually accompanied by considerable polymerization of the diene compound with conjugated bonds, and the yields of the alkylation products are low.

We undertook a systematic study of the alkylation of aromatic compounds with piperylene. Piperylene is a bifunctional alkylating agent and one might expect either the reaction to proceed in stages or the formation of only one final product [4].



In the first case it would be important to establish the possibility of addition in the 1,4-position, the difference in the activities of the double bonds in the 1,2- and 3,4-positions, and the order of addition, i.e., whether it is in accordance or contrary to the electron density distribution in the piperylene molecule. Six products could be formed theoretically and two of these, (I) and (III), have the same structure.



With substituted benzenes there is also the possibility of isomers due to different orientation of the pentenyl group, while in addition to diarylpentanes (VII), the high-boiling substances could contain polypentenyl derivatives of benzene and its substituted derivatives [5].

With the system of conjugated bonds present in the piperylene molecule, in accordance with its polarity [2], a stepwise reaction with addition in the 1,4-position and the formation of product (I) seemed more probable in the presence of acid catalysts.

In actual fact, we were able to confirm that this reaction proceeds stepwise: Under mild conditions, the process could be stopped at the formation of pentenyl derivatives, while diarylpentanes were obtained under more drastic conditions [6]. Alkenylation gives high yields (up to 92%) with aromatic compounds containing sufficiently labile hydrogen atoms in the nucleus, for example, anisole; in the case of benzene, the main direction of the process was polymerization of piperylene [7]. A series of catalysts based on boron trifluoride [BF_3 , $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$, $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$], aluminum chloride (AlCl_3 , $\text{AlCl}_3 \cdot \text{H}_2\text{PO}_4$), and phosphoric and sulfuric acids was tested.

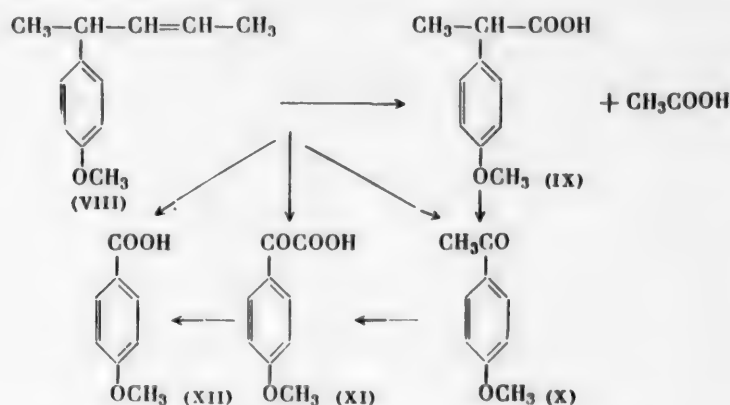
In the present communication we describe experiments on the alkenylation of anisole with piperylene in the presence of boron trifluoride ethyl etherate. The reaction was accompanied by the formation of a considerable amount of high-boiling substances, and the pentenylanisole yields did not exceed 56-62%.

The alkenylation was best carried out at 0 to 20° with the gradual addition of piperylene to a mixture of anisole and catalyst. Dilution of the piperylene with excess anisole (up to 3.5-4 moles) and the reaction time (the optimal time was about 50 hr) had a substantial effect on the pentenylanisole yield. A change in the amount of catalyst from 0.1 to 0.3 mole had little effect on the pentenylanisole yield, which remained within the range of 57-59%. Heating the reaction mixture or increasing the amount of boron trifluoride ethyl etherate at the given dilution and also carrying out the condensation with equimolecular amounts of anisole and piperylene promoted the accumulation of high-boiling products (see Table 1).

Alkylation products obtained in experiments at room temperature and with heating were examined separately. It was impossible to separate the isomers of pentenylanisole by distillation on a column. All the fractions isolated were therefore studied (see Table 2).

Oxidation, bromination, and synthesis were used to establish the structure of the pentenylanisole. Oxidation of pentenylanisole with potassium permanganate in acetone gave good yields of p-methoxyhydratropic acid (IX) and p-methoxyacetophenone (X); acetic acid was also shown to be present by a qualitative reaction. Substance (X) was also isolated in an oxidation by chromic mixture. Oxidation with a 5% solution of potassium permanganate gave a mixture of anisic (XI) and p-methoxybenzoylformic acids (XII); in individual experiments (with the addition of alkali) the yield of the latter reached 50%. In an oxidation by dilute nitric acid, anisic acid was obtained together with nitration products.

Thus, depending on the conditions and the oxidant, almost all of the intermediate products of the oxidation of pentenylanisole to anisic acid were obtained.



No o-methoxybenzoic acid or other oxidation products with ortho substituents were detected. The oxidation products isolated indicated that the pentenylanisole obtained in the presence of boron trifluoride ethyl etherate was mainly 4-(p-methoxyphenyl)-2-pentene (VIII). This was also indicated by bromination of the same fractions: They all gave the same crystalline products, namely the dibromide of 4-(p-methoxyphenyl)-2-pentene (see Table 2). The latter was identified by a mixed melting point with 2,3-dibromo-(p-methoxyphenyl)-pentane, obtained from a synthetic sample of (VIII). 4-(p-Methoxyphenyl)-2-pentene was synthesized by the Grignard-Wurtz reaction in 64% yield, calculated on the starting p-bromoanisole.



Thus, the reaction of anisole with piperylene in the presence of boron trifluoride ethyl etherate proceeds in accordance with the polarity of the piperylene and most probably in the 1,4-position (I). It was impossible to detect products from addition in the 3,4-position (III) or from addition contrary to the electron density distribution in the piperylene molecule (II, IV, and VI). The pentenyl radical mainly entered the position para to the methoxyl group.

Alkenylation of the aromatic nucleus with piperylene is one of the simplest methods of preparing pentenyl derivatives of substituted benzenes with the double bond in the allyl position.

EXPERIMENTAL

For the condensations we used technical piperylene, which had been washed repeatedly with water and a 5% solution of Mohr's salt and distilled over sodium (b.p. 41.5-42.5°, n_D^{20} 1.4245, d_4^{20} 0.6795); commercial anisole

(b.p. 151-152°, n_D^{20} 1.5178, d_4^{20} 0.9932); boron trifluoride ethyl etherate (b.p. 126-127.5°), prepared by the usual method [3] by saturation of absolute ether with boron trifluoride.

The alkylation of anisole with piperylene was carried out in a three-necked flask fitted with a mechanical stirrer, dropping funnel, thermometer, and reflux condenser. To prevent the loss of piperylene, the dropping funnel was cooled with ice and fitted with a reflux condenser; both condensers were closed with calcium chloride tubes. The reaction mixture was stirred vigorously during the introduction of the piperylene and for the next 5-6 hr, and then the mixture was left at room temperature without stirring. A temperature of 0-20° was maintained during the addition of piperylene by control of the input rate (6.8 g of piperylene was added to 10 ml of anisole over a period of 30 min to 2 hr) and by cooling the reaction mixture. During the reaction the mixture turned yellow and then orange or cherry red. The complex was decomposed by treating the mixture with water, and the aqueous layer was extracted with ether. The combined extracts were washed with water, sodium carbonate solution, and again with water. After the extract had been dried with calcium chloride and the ether and excess anisole removed (in vacuum on a water bath), the residue was vacuum distilled from a Favorskii flask. The pentenylanisole fraction consisted of a colorless, mobile liquid with a characteristic odor; it had b.p. 94-97° (4 mm), 87-90° (2 mm), n_D^{20} 1.5165-1.5194. The higher-boiling products were colorless or slightly yellowish oils, which were much more viscous than pentenylanisole. A semi-solid or solid resin remained in the flask. The conditions and results of the most characteristic experiments are given in Table 1 (a total of about 50 experiments was carried out).

Combined portions of pentenylanisoles obtained at 0-20° were vacuum distilled repeatedly on a column. The fractions isolated are given in Table 2.

The oxidation of pentenylanisole with potassium permanganate in acetone was carried out by adding 12.6 g of finely ground permanganate to 5.23 g of pentenylanisole in 125 ml of acetone and 10 ml of water over a period of 9-10 hr with slight cooling and vigorous stirring. When the potassium permanganate had been added, the mixture was stirred for a further 2-3 hr and left overnight. The color of the permanganate had disappeared by next morning. The manganese dioxide was removed and washed with acetone and several times with hot water. The acetone and aqueous solutions were treated separately. From the acetone solution (the products were separated into acid and neutral parts by the usual method) we isolated p-methoxyhydratropic acid (crystallized only after strong cooling). Evaporation and acidification of the aqueous solution yielded further amounts of the acid. After the samples of acid had been combined and recrystallized from a mixture of diethyl ether and ligroin or a very large amount of water, the melting point of the acid corresponded to literature data [11]. The neutral part of the oxidation product, which was either vacuum distilled or used in the crude state for the preparation of 2,4-dinitrophenylhydrazones, consisted of p-methoxyacetophenone. It was identified by a mixed melting point of the 2,4-dinitrophenylhydrazones obtained from the neutral part and p-methoxyacetophenone synthesized from anisole and acetic anhydride [8]. The results of oxidation of separate fractions of pentenylanisole are given in Table 2.

Oxidation of pentenylanisole with 5% potassium permanganate solution (without addition of alkali). Over a period of 10-12 hr, 16 g of potassium permanganate was added to 2.64 g of pentenylanisole with vigorous stirring. For complete decolorization, the mixture was heated on a water bath for 2-4 hr. The manganese dioxide was removed by filtration and washed repeatedly with hot water; the mother solution was evaporated to 40-60 ml and acidified with 50% sulfuric acid. The white, voluminous precipitate of anisic acid was collected, dried, and weighed (the crude anisic acid melted over the range 179-182°). The acid was recrystallized from aqueous alcohol and identified by a mixed melting point with anisic acid obtained from p-bromoanisole by organomagnesium synthesis [9]. Further evaporation of the acid solution precipitated p-methoxybenzoylformic acid (XI) as a difficultly crystallizable oil. Still further evaporation gave a mixture of the oily acid (XI) and inorganic salts, which were separated by extraction with ether or chloroform. With careful fractional evaporation of the acid solution, p-methoxybenzoylformic acid could be isolated in a crystalline state. It was converted into anisic acid by treatment with 30% hydrogen peroxide [10]. Data on the oxidation of pentenylanisole fractions with 5% potassium permanganate solution are given in Table 2.

Oxidation with 4% potassium permanganate solution in an alkaline medium. To 2.64 g of pentenylanisole and 3 g of caustic alkali in 55 ml of water was added 16 g of potassium permanganate (6 g as a 4% solution and the rest as a powder). The acids were isolated in the same way as in the oxidation without the addition of alkali. The results of oxidation of the three main pentenylanisole fractions are given below.

TABLE 1

Alkylation of Anisole with Piperylene in the Presence of Boron Trifluoride Ethyl Etherate (6.8 g or 0.1 mole of piperylene was used in each experiment)

Molar ratios of piperylene: anisole: boron trifluoride ethyl etherate	Reaction time (hr)	Pentenyl-anisole yield (%)	Yield of high-boiling products (g)	Still residue (g)	Content of high-boiling products, including distillation residue, relative to sum of substances obtained (%)
1:1:0.01	50	8.2	1.4	1.2	64.0
1:1:0.10	51	25.8	4.6	2.2	59.9
1:3.7:0.015	48	12.2	—	1.0	35.7
1:3.7:0.03	74	19.5	1.2	1.9	36.9
1:3.7:0.06	52	53.7	2.8	1.8	32.4
1:3.7:0.10	7	38.4	2.8	0.4	32.1
1:3.7:0.10	20	44.3	2.4	2.4	35.0
1:3.7:0.11	50	56.8	2.3	0.6	22.8
1:3.7:0.11	123	54.8	3.6	0.9	31.6
1:3.7:0.11*	18	32.9	7.25	4.0	66.0
1:3.7:0.10**	15	25.8	11.8	1.0	73.3
1:3.7:0.20	52	57.2	3.1	0.6	31.5
1:3.7:0.25	50	58.8	3.8	0.7	30.3
1:10:0.25	58	62.4	3.6	1.1	30.1
1:3.7:0.3	50	57.5	4.2	0.5	31.7
1:3.7:0.4	53	51.8	4.0	0.7	33.9
1:3.7:0.6	50	45.1	4.3	1.4	41.3

* The mixture was heated at 50-70° for 3 hr.

** The mixture was heated at 50-60° for 1 hr and at 98° for 1.5 hr.

TABLE 2

Demonstration of Structure of Pentenylanisole Obtained at 0-20°

Results of distillation of combined pentenylanisole samples				Yield of dibromide with m.p. 73-74° (%)	Yield of products from potassium permanganate oxidation (%)			
boiling point (pressure in mm)	yield (g)	n_D^{20}	d_4^{20}		5% solution	in acetone		
					anisic acid, m.p. 182-183*	p-methoxybenzoic acid	p-methoxybenzoic acid, m.p. 56-57**	p-methoxyacetophenone***
64-76° (1)	0.69	1.5165	—	—	—	—	—	—
78-80 (1)	9.11	1.5170	0.9509	51.0	35.6	16.7	—	—
86.5-87 (1) ****	62.6	1.5178	0.9513	53.2	28.2	21.1	42.3	44.3
87-90 (1.5)	18.90	1.5180	0.9512	56.6	30.1	23.7	38.3	60.0
88-88.2 (1.5) *****	53.2	1.5182	0.9513	91.2	43.9	21.1	38.0	46.4
76-78 (0.5)	5.91	1.5165	0.9517	80.4	13.2	—	—	—
76 (0.2)	0.90	1.5178	0.9540	56.7	—	—	—	—
76-77 (0.2)	1.02	1.5175	0.9580	18.7	—	—	—	—

* Literature data [16]: m.p. 184°.

** Literature data [11]: m.p. 57°.

*** 2,4-Dinitrophenylhydrazon, m.p. 219-220°; literature data [12]: m.p. 220°.

**** Found %: C 81.58; H 8.91, 9.05. $C_{12}H_{16}O$. Calculated %: C 81.77; H 9.16.

***** Found %: C 81.51, 81.87; H 9.40, 9.56. $C_{12}H_{16}O$. Calculated %: C 81.77; H 9.16.

Oxidation of the 3rd fraction without subsequent heating of the reaction mixture gave 0.33 g (14.5%) of anisic acid with m.p. 182-183° (from aqueous alcohol) and 1.37 g (50.7%) of p-methoxybenzoylformic acid with m.p. 83-86° (m.p. 90-91° after recrystallization).

Literature data: for anisic acid [16], m.p. 184°, for p-methoxybenzoylformic acid [11], m.p. 93°.

Oxidation of the 4th fraction with subsequent heating of the reaction mixture to boiling yielded 0.36 g (15.8%) of anisic acid with m.p. 182-182.5° and 0.5 g (22.3%) of crude p-methoxybenzoylformic acid with m.p. 82-90°. Treatment of the latter with hydrogen peroxide yielded 0.46 g of anisic acid with m.p. 178-180° (20.3% on the starting pentenylanisole and 91% on the p-methoxybenzoylformic acid).

Oxidation of the 5th fraction with subsequent heating of the reaction mixture on a water bath yielded 0.98 g (43%) of anisic acid with m.p. 181-182° and 0.36 g (13%) of p-methoxybenzoylformic acid with m.p. 91-92° (from water). Treatment of the latter with 30% hydrogen peroxide yielded anisic acid with m.p. 178.5-179.5°.

Oxidation of pentenylanisole with potassium bichromate. Heating a mixture of 1.76 g of the 3rd fraction, 8.09 g of potassium bichromate, 35 ml of water, and 9.6 ml of concentrated sulfuric acid for 3 hr yielded 0.7 g (46.8%) of crude p-methoxyacetophenone. The 2,4-dinitrophenylhydrazone had m.p. 211-212°; a mixture with the 2,4-dinitrophenylhydrazone of synthetic p-methoxyacetophenone melted at 214-215°. A small amount of anisic acid with m.p. 182° was isolated from the acid part.

Oxidation of pentenylanisole with nitric acid. Heating 1 g of the 3rd fraction with 75 ml of 25% nitric acid gave anisic acid with m.p. 182-184° (after sublimation and repeated recrystallization from aqueous alcohol).

Bromination of pentenylanisole. The calculated amount of bromine in the form of a 4% solution in chloroform was added in the dark with cooling to 2.64 g of pentenylanisole in a fivefold amount of chloroform. The chloroform was removed in vacuum on a water bath and the residue crystallized (crystallization began instantly when a seed of the dibromide was introduced). The crystals were collected, washed with a small amount of anhydrous alcohol, dried, and weighed. On prolonged standing, the mother liquor deposited a further amount of the dibromide (distillation of the residue after removal of the chloroform in vacuum gave similar results). The dibromide crystallized in the form of white lustrous leaflets (from anhydrous alcohol). The yields are given in Table 2. The product was identified by a mixed melting point with synthetic 2,3-dibromo-(p-methoxyphenyl)-pentane.

Synthesis of 4-(p-Methoxyphenyl)-2-pentene

4-Chloro-2-pentene [13]. Saturation of 35.3 g of piperylene with dry, gaseous hydrogen chloride with cooling gave 38.6 g (78.8%) of a fraction with b.p. 30-32° (65 mm). After being washed with water, dried with calcium chloride, and redistilled, the substance had the following constants:

B.p. 102-103°, n_D^{20} 1.4335, d_4^{20} 0.9001, M_R 29.52. C_5H_9Cl . Calculated 29.79. Literature data [13, 14]: b.p. 96-97°, n_D^{20} 1.4320-1.4328, d_4^{20} 0.9001-0.9004.

p-Bromoanisole was obtained by the Sandmeyer reaction [15] from 62 g of p-anisidine. The yield was 39.8 g (84.5%).

B.p. 94-96° (15 mm), n_D^{20} 1.5602, d_4^{20} 1.4656.

Literature data [16]: b.p. 100° (16 mm), n_D^{20} 1.5605, d_4^{20} 1.457.

4-(p-Methoxyphenyl)-2-pentene. A solution of 21.2 g of 4-chloro-2-pentene in 40 ml of absolute ether was added over a period of 2 hr with cooling to the organomagnesium compound from 30.6 g of p-bromoanisole and 4.8 g of magnesium in 180 ml of absolute ether, and then the mixture was heated on a water bath for 2 hr and treated with 10% hydrochloric acid. Vacuum distillation of the residue (after drying and removal of the solvent) gave 28.4 g (64%) of 4-(p-methoxyphenyl)-2-pentene, which boiled at 124-130° (15 mm). Treatment with alkali and redistillation gave a colorless liquid.

B.p. 83-86° (3 mm), n_D^{20} 1.5190, d_4^{20} 0.9512, M_R 56.24. $C_{12}H_{16}O$. Calculated 55.19.

Oxidation of 2.64 g of 4-(p-methoxyphenyl)-2-pentene gave 1.06 g (46.2%) of crude anisic acid with m.p. 180-181° and 0.1 g (3.7%) of p-methoxybenzoylformic acid as an oil.

2,3-Dibromo-(p-methoxyphenyl)-pentane. From 3.57 g of 4-(p-methoxyphenyl)-2-pentene in 15 ml of chloroform and 3.5 g of bromine in the form of a 4% solution in chloroform we obtained 6.0 g (93.3%) of the dibromide. The white lustrous crystals had m.p. 73-74° (from alcohol).

Found %: C 42.82, 42.64; H 4.90, 5.07; Br 47.40. $C_{12}H_{16}OBr_2$. Calculated %: C 42.88; H 4.80; Br 47.56.

SUMMARY

1. The alkylation of anisole with piperylene in the presence of boron trifluoride ethyl etherate was studied.
2. It was shown that anisole may be alkenylated in the nucleus with piperylene to give up to 62% of pentenyl-anisole.
3. The effect of various factors on the pentenylanisole yield and the ratio of pentenylanisole to high-boiling reaction products was established.
4. The main alkenylation product was 4-(p-methoxyphenyl)-2-pentene.
5. 4-(p-Methoxyphenyl)-2-pentene was prepared by an unequivocal synthesis and 2,3-dibromo-(p-methoxyphenyl)-pentane was obtained.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

ALKYLATION OF AROMATIC COMPOUNDS WITH DIENES

II. ALKENYLATION OF ANISOLE WITH PIPERYLENE IN THE PRESENCE OF BORON TRIFLUORIDE, ALUMINUM CHLORIDE, AND THEIR COMPOUNDS WITH ORTHOPHOSPHORIC ACID

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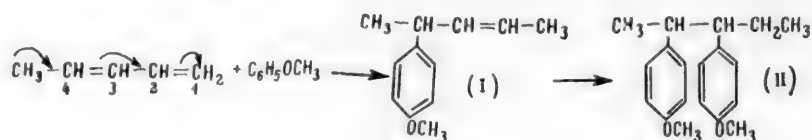
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We established the main features of the alkylation of anisole with piperylene using boron trifluoride ethyl etherate as the catalyst [1]. As a diene compound with conjugated bonds, piperylene reacts predominantly in the 1,4-position in accordance with the electron density distribution to form pentenylanisole, which consists mainly of 4-(p-methoxyphenyl)-2-pentene (I) [1, 2].



The optimal conditions for alkenylation of the nucleus were found to be a temperature of 0-20°, dilution of the piperylene with anisole in the proportion of 3.5-4 moles per mole of piperylene, the use of 0.1-0.3 mole of catalyst, and a reaction time of 50 hr.

However, we were unable to obtain pentenylanisole in more than 62% yield. We therefore attempted to obtain higher yields of pentenylanisole by the use of other catalysts.

In the present work we describe the alkylation of anisole with piperylene in the presence of boron trifluoride, anhydrous orthophosphoric acid, the molecular compound of boron trifluoride and orthophosphoric acid, aluminum chloride, and the product of its reaction with phosphoric acid, $\text{AlCl}_3 \cdot \text{H}_2\text{PO}_4$, which was proposed in a patent [3].

The molecular compound of boron trifluoride and orthophosphoric acid is regarded as one of the best catalysts for the alkylation of aromatic compounds with olefins [4]. Therefore, despite the strong polymerizing action of this catalyst in comparison with boron trifluoride ethyl etherate, it seemed interesting to use it in the alkylation with diolefins with conjugated bonds, the more so as the alkenylation of toluene with piperylene in the presence of this catalyst has been reported in a patent [5]. Attempts to use aluminum chloride in condensations of this type have been reported in the literature [6, 7]. However, the use of such a vigorous catalyst leads to polymerization of the diene, and low-molecular compounds are formed only in very small amounts.

We were able to alkenylate the aromatic nucleus with all the given catalysts (Tables 1 and 2). The best results were obtained with the mildest catalyst, namely anhydrous orthophosphoric acid. Alkylation in the presence of phosphoric acid was characterized by the complete absence of by-products, and high yields, regardless of the reaction conditions. The process could be accelerated by brief heating of the reaction mixture to 40-45°. Quite high yields of pentenylanisole, higher than with $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$, could also be obtained with such active catalysts as $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$, BF_3 , and AlCl_3 . With boron trifluoride, the reaction was accompanied by the formation of a considerable amount of high-boiling products.

The conditions giving an increase in the pentenylanisole yields depended to a large extent on the activity of the catalyst: The more active the catalyst, the milder the conditions had to be, i.e., the smaller the amount of catalyst,

TABLE 1

Alkylation of Anisole with Piperylene in the Presence of 100% Orthophosphoric Acid
(6.8 g of piperylene was used in each experiment)

Molar ratios of piperylene: anisole: phosphoric acid	Heating (after stirring at room temperature)		Total stirring time (hr)	Reaction time (hr)	Pentenyl-anisole yield (%)	Yield of high-boiling products, including distillation residue, relative to the sum of the reaction products (%)
	time (hr)	temperature				
1:4:0.13	—	—	6.5	6.5	52.3	15.8
1:4:0.20	—	—	10.5	50	76.0	11.2
1:5:0.25	—	—	3	3	37.5	24.1
1:4:0.25	—	—	7	20.5	83.8	14.1
1:4:0.25	—	—	8	8	86.8	—
1:4:0.25	—	—	9	9	88.6	7.5
1:4:0.25	—	—	13.5	50	92.2	8.6
1:5:0.25	2	35—40°	6.5	6.5	71.7	10.4
1:4:0.25	1	40—50	5	5	77.3	8.1
1:5:0.25	1	50	3.5	3.5	80.5	8.2
1:4:0.25*	—	—	8	50	44.6	9.4
1:5:0.25**	—	—	9	9	71.3	21.7***

* 85% orthophosphoric acid.

** Concentrated sulfuric acid.

*** From the fraction with b.p. 180–200° (2.5 mm) we isolated 2,3-bis-(p-methoxyphenyl)-pentane with m.p. 107–108° [8].

TABLE 2

Alkylation of Anisole with Piperylene in the Presence of BF_3 , $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$, AlCl_3 , $\text{AlCl}_3 \cdot \text{H}_3\text{PO}_4$
(6.8 g of piperylene was used in each experiment)

Catalyst	Molar ratios of piperylene: anisole: catalyst	Reaction time (hr)	Yield		Yield of high-boiling products, including distillation residue, relative to the sum of the reaction products (%)
			reaction products (g)	pentenyl-anisole (%)	
BF_3	1:4:0.04	4	6.8	22.5	41.7
BF_3	1:4:0.10	1.5	15.7	65.4	26.7
BF_3	1:5:0.10	1.5	15.0	53.4	37.3
BF_3	1:5:0.10	3.5	15.7	66.9	25.1
BF_3	1:10:0.25	3.5	17.7	59.4	40.7
BF_3	1:4:0.12	6	16.9	58.5	39.0
BF_3	1:4:0.10	24*	17.4	34.1	62.7
BF_3	1:4:0.12	46*	16.3	27.8	69.1**
$\text{BF}_3 \cdot \text{H}_3\text{PO}_4$	1:4:0.10	4	13.0	56.5	24.1
$\text{BF}_3 \cdot \text{H}_3\text{PO}_4$	1:4:0.10	8	14.9	65.4	22.5
$\text{BF}_3 \cdot \text{H}_3\text{PO}_4$	1:10:0.10	8	12.9	55.1	16.8
$\text{BF}_3 \cdot \text{H}_3\text{PO}_4$	1:10:0.25	18	17.6	84.0	13.9
AlCl_3	1:4.5:0.015	3	2.2	12.2	—
AlCl_3	1:4:0.07	2.5	15.4	65.4	25.9
AlCl_3	1:8:0.07	3.5	16.6	66.3	30.6
AlCl_3	1:10:0.08	5	15.4	68.7	21.3
$\text{AlCl}_3 \cdot \text{H}_2\text{PO}_4$	1:4:0.05	6	10.7	47.0	23.0
$\text{AlCl}_3 \cdot \text{H}_2\text{PO}_4$	1:4:0.10	7	14.1	67.7	27.0

* The mixture was stirred for 5 hr and left at room temperature for the rest of the time.

** On standing, the fraction with b.p. 180–200° (2 mm), n_D^{20} 1.5537, deposited crystals with m.p. 106–107.5° (from alcohol), corresponding to 2,3-bis-(p-methoxyphenyl)-pentane [8].

the shorter the reaction time and the greater the dilution. Thus, while in the case of $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$ the yield of the reaction product, which was 56-59% at a dilution of 1: 4, depended little on the amount of catalyst over the range of 0.1-0.3 mole, with phosphoric acid, an increase in the amount of catalyst from 0.1 to 0.25 mole led to an increase in the yields to 89-92%; with BF_3 and $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$, it was necessary to use not more than 0.1 mole of catalyst to avoid the formation of high-boiling products, and with AlCl_3 these amounts were even less (0.07 mole). The pentenyl-anisole yields reached only 65%. The best yields with $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$ could be attained only with a simultaneous increase in the amount of catalyst and dilution; with molar ratios of piperylene: anisole: catalyst of a 1: 4: 0.1 and 1: 10: 0.25, the product yields were 65 and 84%, respectively. Thus, in comparison with phosphoric acid, $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$ required a further increase in the dilution with anisole with the same amounts of catalyst (0.25 mole). Considerable amounts of high-boiling products were formed, and the yield of pentenylanisole was low with boron trifluoride even at these dilutions.

The duration of the process had a very strong effect on the pentenylanisole yield. Under the optimal conditions found for $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$, namely a reaction time of 50 hr and molar ratios of piperylene: anisole: catalyst of 1: 4: 0.1, with boron trifluoride we obtained mainly high-boiling substances, from which it was possible to isolate 2,3-bis-(p-methoxyphenyl)-pentane (II) [8]. The yield of the main product hardly reached 28%. The highest yields of pentenylanisole in the presence of boron trifluoride were obtained with a reaction time of 1.5-3.5 hr (dilution of 1: 4 and 1: 5) and with aluminum chloride, from 2 to 5 hr (dilution of 1: 4 and 1: 10). A reaction time of not less than 8 hr was necessary to obtain the same results with $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$. The pentenylanisole yield was 87-89% after 8-9 hr with anhydrous orthophosphoric acid, and the time that the mixture was stirred was of considerable importance (phosphoric acid is not miscible with the reaction components), while the time that the mixture stood without stirring had practically no effect on the yield. Under the same conditions, 85% phosphoric acid gave much worse results; the pentenylanisole yields were 71% with concentrated sulfuric acid. $\text{AlCl}_3 \cdot \text{H}_2\text{PO}_4$ was similar in catalytic activity to the molecular compound of boron trifluoride and phosphoric acid.

The structure of the pentenylanisoles was demonstrated by bromination of the fractions isolated by fractional distillation of the main product separately for each catalyst and identification of crystalline 2,3-dibromo-(p-methoxyphenyl)-pentane (Table 3). The presence of 4-(p-methoxyphenyl)-2-pentene (I) was confirmed by conversion of the pentenylanisole into crystalline 2,3-bis-(p-methoxyphenyl)-pentane (III) both during the reaction itself (with BF_3 and $\text{AlCl}_3 \cdot \text{H}_2\text{PO}_4$) and by carrying out the reaction in two stages (with $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$). To detect the ortho-isomer, fractions of pentenylanisole were oxidized with 4 and 5% potassium permanganate solution in alkaline and neutral media. However, no o-methoxybenzoic acid could be detected in any case; the oxidation products contained anisic and p-methoxybenzoylformic acids.

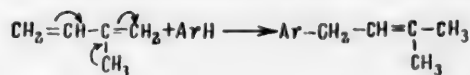
TABLE 3

Results of Oxidation and Bromination of Pentenylanisole Fractions Obtained by Distillation

Catalyst	Boiling point (pressure in mm)	Yield (g)	n_D^{20}	d_4^{20}	Yield of dibromide with m.p. 73-74°*	Yield of oxidation products (%)	
						anisic acid	p-methoxy- benzoylformic acid
BF_3	27-82° (1.5)	1.4	1.5166	—	—	—	—
	83-87 (1.5)	9.3	1.5149	0.9515	25.6	15.5	11.1
	87-90 (1.5-2)	7.7	1.5170	0.9503	61.0	35.4	9.4
	87.2-87.3 (1.5)	8.5	1.5170	0.9509	55.8	27.7	14.4
	84-85 (1)	3.4	1.5166	0.9504	49.1	—	—
	94-96.5 (3)	17.9	1.5170	0.9501	63.4	20.5	21.4
H_3PO_4	97-99.5 (3)	30.0	1.5179	0.9515	64.9	42.6	19.2
	46-78 (0.5)	1.5	1.5138	—	—	—	—
	88.2-90 (3)	17.9	1.5160	0.9492	85.3	21.8	3.0
	90.2-91.2 (3)	12.7	1.5161	0.9492	53.6	50.0	7.4
	88-88.5 (2.5)	1.9	1.5166	0.9501	—	—	—
	78.8-84 (1.5)	29.3	1.5169	0.9512	70.3	—	—
	89-91 (2.5)	35.8	1.5170	0.9513	72.2	33.0	24.0

* Synthetic 2,3-dibromo-(p-methoxyphenyl)-pentane melts at 73-74° [1].

The isolation of substance (I) with all the catalysts studied confirmed the hypothesis put forward previously on the reactivity of piperylene as a bifunctional compound [1]. Alkylation by diolefins, as a particular case of condensation with ethylenic unsaturated hydrocarbons, probably proceeds through the formation of an intermediate complex of the diene with the catalyst or a ternary complex in which the positive charge may be concentrated either on carbon atom 4 or 2, which gives identical products in the case of piperylene. The formation of the product of 1,4- and not 1,2-addition agrees with the results of alkenylation with other dienes where isomers obtained by addition in the 1,2- and 1,4-positions are readily distinguished, for example, with butadiene [7, 9], isoprene [10], dimethylbutadiene [11], and cyclopentadiene [12]. It is also characteristic that with isoprene, which, like piperylene, is not a symmetrical diolefin, the order of addition in the 1,4-position corresponds to the electron density distribution in the molecule.



At the same time, the literature contains reports on the formation of other isomers, for example, $\text{CH}_3-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-\text{Ar}$. This structure was assigned to the products from alkenylation of toluene [5] and trimethylhydroquinone [13] with piperylene, and in the latter case the authors considered that they isolated 5,6,8-trimethyl-2-ethyl-6-hydroxychroman. It seems to us that these data require checking, as reliable methods of demonstrating the structure were not used in the work.

EXPERIMENTAL

The alkylation of anisole with piperylene was carried out by the procedure described previously [1]. In experiments with free boron trifluoride, the anisole was saturated directly in the reaction flask. AlCl_3 and $\text{AlCl}_3 \cdot \text{H}_2\text{PO}_4$ were added gradually to a mixture of anisole and piperylene. The purification and characteristics of the starting materials were given in [1]. The molecular compound of boron trifluoride and orthophosphoric acid was prepared by passing boron trifluoride into 100% H_3PO_4 (d 1.88) until the required increase in weight was reached. Boron trifluoride was obtained from calcium fluoride, boric anhydride, and concentrated sulfuric acid [4]. The aluminum chloride was used without further purification. The catalyst $\text{AlCl}_3 \cdot \text{H}_2\text{PO}_4$ was obtained in accordance with the patent [3] by mixing equimolecular amounts of anhydrous AlCl_3 and 100% H_3PO_4 and then heating the mixture to 80° until the evolution of hydrogen chloride ceased completely. The product was an almost white, porous mass, which was less hygroscopic than aluminum chloride. More than 50 experiments were carried out, and the most characteristic are given in Tables 1 and 2.

Combined portions of pentenylanisole for each catalyst separately were vacuum distilled on a column, but it was impossible to isolate individual isomers. Table 3 gives the fractions obtained by distillation of pentenylanisoles prepared with boron trifluoride and phosphoric acid and also the results of bromination and oxidation with 5% potassium permanganate solution [1]. In the case of $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$ and AlCl_3 , 4 fractions were isolated in each distillation and with $\text{AlCl}_3 \cdot \text{H}_2\text{PO}_4$, 3 fractions; they all had similar constants and gave similar results on oxidation and bromination and therefore are not given in the table.

The dibromides were identified by a mixed melting point with 2,3-dibromo-(p-methoxyphenyl)-pentane, which we obtained from synthetic 4-(p-methoxyphenyl)-2-pentene [1], and the anisic acid by a mixed melting point with a synthetic sample prepared from p-bromoanisole by organomagnesium synthesis [14]. Synthetic 2,3-dibromo-(p-methoxyphenyl)-pentane melted at 73-74° and the anisic acid at 183-184° [15]. p-Methoxybenzoylformic acid, which was isolated as an oil in most experiments, was identified by its conversion to anisic acid by treatment with 30% hydrogen peroxide [16]. The yield of p-methoxybenzoylformic acid was considerably higher with oxidation in an alkaline medium and it could be isolated in a crystalline form. Experiments on the oxidation of pentenylanisole fractions obtained in the presence of phosphoric acid with potassium permanganate in an alkaline medium [1] are given below.

a) The oxidation of 3.52 g of the 3rd fraction with 4 g of caustic alkali in 80 ml of water and 21 g of potassium permanganate (12 g in the form of a 4% solution and the rest as a powder) with subsequent heating on a water bath yielded 2.2 g of white crystals (on freezing in snow) and 0.45 g (12.6%) of p-methoxybenzoylformic acid as an oil. Recrystallization of the main portion gave 0.09 g (3.1%) of anisic acid (m.p. 182-183°) and the rest of the crystals were p-methoxybenzoylformic acid with m.p. 89-90°, which corresponds to literature data [15]. Treatment of the acid with hydrogen peroxide yielded anisic acid (m.p. 180-181.5°).

b) Oxidation of 3.53 g of the 2nd fraction gave, after recrystallization, 11.1% of anisic acid (m.p. 182-183°) and 31% of p-methoxybenzoylformic acid (m.p. 83-84°). Treatment of 0.37 g of crystalline p-methoxybenzoylformic acid with hydrogen peroxide yielded 0.33 g (84%) of anisic acid (m.p. 181.5-182.5°).

Alkylation of anisole with pentenylanisole in the presence of $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$. Heating a mixture of 19.8 g of pentenylanisole, obtained with phosphoric acid, 23.3 g of anisole, and 3.58 g of $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$ on a water bath with stirring for 2 hr yielded 10.25 g (33.4%) of a dianisylpentane fraction.

B.p. 190-207° (8 mm), n_D^{20} 1.5610, d_4^{20} 1.0590, M_R 86.76. $\text{C}_{19}\text{H}_{24}\text{O}_2$. Calculated 86.03.

On addition of anhydrous alcohol and freezing, the bulk of the substance crystallized. We isolated white needlelike crystals of 2,3-bis-(p-methoxyphenyl)-pentane with m.p. 106-107° (from alcohol) [8].

SUMMARY

1. The alkylation of anisole with piperylene in the presence of $\text{BF}_3 \cdot \text{H}_3\text{PO}_4$, BF_3 , H_3PO_4 , AlCl_3 , $\text{AlCl}_3 \cdot \text{H}_2\text{PO}_4$, and H_2SO_4 was studied. It was shown that anisole may be alkenylated with piperylene to give pentenylanisoles in a yield of 65-92%. The best catalyst for the alkenylation of anisole with piperylene was anhydrous orthophosphoric acid.

2. It was shown that the main alkenylation product with all the catalysts used was 4-(p-methoxyphenyl)-2-pentene. The reaction of anisole with piperylene proceeds in accordance with the polarity of piperylene and predominantly in the 1,4-position, regardless of the nature of the acid catalyst.

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SYNTHETIC ANESTHETICS

SEPARATION OF STEREOISOMERIC 1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDOLS

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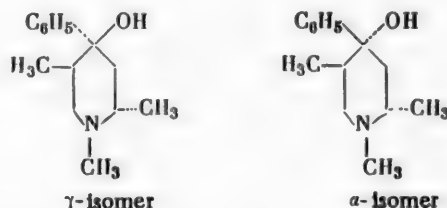
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On the basis of experimental data, we previously [1, 2] put forward some considerations on the steric structure of the known effective analgesics promedol and α -promedol, which are esters of the γ - and α -isomers, respectively, of 1,2,5-trimethyl-4-phenyl-4-piperidol [3, 4]. It was proposed that the isomeric γ - and α -1,2,5-trimethyl-4-phenyl-4-piperidols are derivatives of trans-1,2,5-trimethyl-4-piperidone and differ from each other in the position of the phenyl radical and hydroxyl group at the fourth carbon atom of the piperidine ring.

In the γ -isomer (the piperidol corresponding to promedol) the phenyl radical at C_4 and the methyl group at C_5 are in the trans position. In the α -isomer (the piperidol corresponding to α -promedol) these substituents occupy the cis positions.



In examining various ways of preparing promedol, α -promedol, and isopromedol, we studied the separation of the stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols by chromatography on alumina. Through identical chromatography columns filled with alumina were passed solutions of 1.5 g of each of the stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols in chloroform and the sequence of their elution from the column determined.

The displacement volumes in the elution of the isomeric 1,2,5-trimethyl-4-phenyl-4-piperidols were 60 ml for the γ -isomer, 75 ml for the β -isomer, and 105 ml for the α -isomer (Fig. 1).

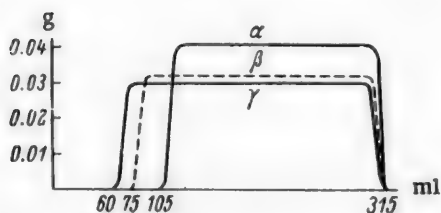


Fig. 1. Elution of isomeric 1,2,5-trimethyl-4-phenyl-4-piperidols (adsorbent Al_2O_3 , solvent $CHCl_3$).

We studied the separation of mixtures of equal amounts (0.75 g of each) of two stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols ($\alpha + \beta$, $\alpha + \gamma$, and $\beta + \gamma$) on the same chromatographic columns (Fig. 2).

As was to be expected, the β -isomer was eluted first from the mixture of α - and β -piperidols and then the α -isomer. First the γ -isomer and then the α -isomer were eluted from the mixture of α - and γ -piperidols, and the sequence of elution from the mixture of β - and γ -piperidols was first the γ - and then the β -isomer. In the latter case there was not such sharp separation as with the mixtures given above. After the first fractions, which contained the γ -isomer, a mixture of isomeric piperidols ($\sim 30\%$) was eluted and then the β -isomer.

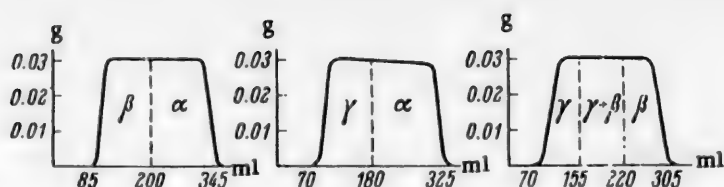
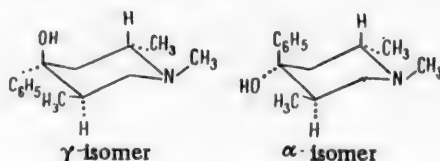


Fig. 2. Separation of binary mixtures of 1,2,5-trimethyl-4-phenyl-4-piperidols by chromatography.

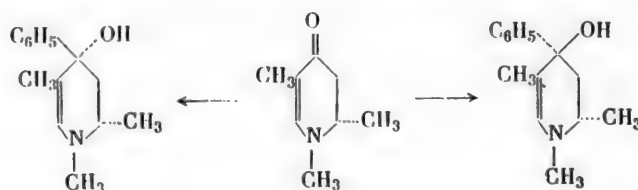
Consequently, the isomeric 1,2,5-trimethyl-4-phenyl-4-piperidols are adsorbed on alumina to different extents, and these are determined by their steric structure. Chromatography is sometimes used as an additional method of demonstrating the configuration of stereoisomeric alcohols and their ethers. On a large number of examples, especially in the steroid series, it has been established that alcohols with an equatorial hydroxyl group are adsorbed more strongly and consequently are more difficult to elute from a chromatography column than alcohols with an axial hydroxyl group [5].

On the basis of this principle of conformational analysis and the results given above it may be concluded that in the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol, which is adsorbed more strongly by alumina, the hydroxyl group occupies an equatorial position and the γ -isomer, which is eluted from a chromatography column much more rapidly than the α -isomer, contains an axial hydroxyl group.

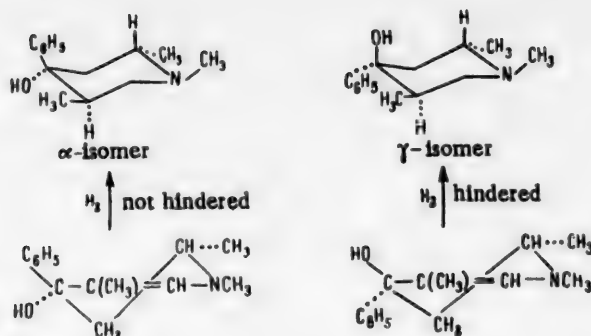


There was evidently no conversion of the piperidine ring during chromatography of the α - and γ -isomers of the piperidol. The conversion form of the γ -isomer should be extremely unstable due to the axial position of all the substituents apart from the hydroxyl group. The formation of the conversion form of the α -isomer, in which the phenyl radical occupies an equatorial position, is more probable. However, in this case there should be no sharp difference in the adsorption of the γ - and α -isomers of the piperidol as they would both have equatorial hydroxyl groups.

The synthesis of the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol from 1,2,5-trimethyl- Δ^5 -didehydro-4-piperidone was described in a paper published recently [6]. This piperidone and phenyllithium yielded 1,2,5-trimethyl-4-phenyl- Δ^5 -didehydro-4-piperidol, which yielded the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol on catalytic hydrogenation. Theoretically, the reaction of phenyllithium with 1,2,5-trimethyl- Δ^5 -didehydro-4-piperidone can form two stereoisomeric 1,2,5-trimethyl-4-phenyl- Δ^5 -didehydro-4-piperidols.



Only one isomer of 1,2,5-trimethyl-4-phenyl- Δ^5 -didehydro-4-piperidol was isolated in the synthesis and this was hydrogenated catalytically. Since the structure of the 1,2,5-trimethyl-4-phenyl- Δ^5 -didehydro-4-piperidol was not established, its subsequent conversions must be considered on the basis of the two theoretically possible stereoisomeric forms given above. The catalytic hydrogenation of each of these isomers may form two isomeric piperidols belonging to the trans series with respect to the position of the methyl groups relative to the piperidine ring and two belonging to the cis series. As the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol belongs to the trans series, of all the possible isomeric piperidols which could be formed by hydrogenation of 1,2,5-trimethyl-4-phenyl- Δ^5 -didehydro-4-piperidol, we will examine only those that have the methyl groups in the same position relative to the piperidine ring (the stereochemistry of the β -isomer will be considered separately).



The possibility of the formation of one of these two piperidols in the catalytic hydrogenation of 1,2,5-trimethyl-4-phenyl- Δ^5 -didehydro-4-piperidol is determined by steric factors which affect the adsorption of this unsaturated compound by the catalyst and steric factors affecting the addition of hydrogen. The adsorption of 1,2,5-trimethyl-4-phenyl- Δ^5 -didehydro-4-piperidol and also the addition of hydrogen are hindered from the side of the ring on which the phenyl radical lies, while the other side of the ring is not sterically hindered in this respect (one of the possible conformations of the unsaturated piperidols is illustrated in the scheme).

Consequently, if we consider the steric structure of 1,2,5-trimethyl-4-phenyl- Δ^5 -didehydro-4-piperidol and also that there is *cis* addition of hydrogen in the catalytic hydrogenation, then in the hydrogenation of the unsaturated piperidol examined one might expect the formation of 1,2,5-trimethyl-4-phenyl-4-piperidol with the phenyl radical at C₄ and the methyl group at C₅ in the *cis* position. This structure corresponds to the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol, which was actually isolated in this synthesis.

Promedol and α -promedol are formed by treatment of γ - and α -1,2,5-trimethyl-4-phenyl-4-piperidols, respectively, with propionyl chloride. Promedol preparations obtained in this way are readily purified by recrystallization from acetone or alcohol. However, samples of α -promedol isolated in this way normally melt at a lower temperature and over wide ranges (96-103, 98-108, 103-109, 106-108, 107-112, 126-131°). Successive recrystallizations from acetone or alcohol do not lead to a substantial change in the melting point. After trying various solvents, we established that the hydrochloride of the propionate of the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (α -promedol) dissolves in benzene and partially in toluene. By using benzene for the recrystallization of α -promedol, we obtained a sample of the latter with m.p. 153-154°.

It should be noted that the α -promedol samples we isolated (with m.p. 106-107, 126-131, and 153-154°) were found to be identical pharmacologically. Their anesthetic activities were approximately 2-2.5 times greater than that of promedol and almost equal to that of isopromedol. They were also equivalent in toxicity*.

Hydrolysis of all these samples of α -promedol yielded the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol.

EXPERIMENTAL

The determination of the displacement volumes of stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols (1.5 g) on passing through a chromatography column is given in Table 1.

The separation of binary mixtures of isomeric 1,2,5-trimethyl-4-phenyl-4-piperidols by chromatography on alumina is given in Table 2.

The isolation of the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol from a mixture of the isomeric α -, β -, and γ -piperidols by chromatography on alumina is given in Table 3.

Propionate of the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (α -promedol). To 12 g of the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 106-107°), 0.5 g of magnesium, and 120 ml of anhydrous benzene was

* These preparations were examined pharmacologically by M. D. Mashkovskii.

TABLE 1

Isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol	Number of fractions taken	Total volume of solution emerging from column (ml)	Amount of piperidol isolated (g)	Displacement volume (ml)
γ	12	60	—	60
	45	225	1.44	
	5	25	Traces	
	3	15	—	
β	15	75	—	75
	42	210	1.49	
	6	30	Traces	
	2	10	—	
α	21	105	—	105
	38	190	1.43	
	4	20	Traces	
	2	10	—	

Footnote: The column was 50 cm in height and 1.5 cm in diameter and the weight of alumina was 69 g. The solvent was chloroform. The volume of the fractions collected was 5 ml.

TABLE 2

Isomeric 1,2,5-trimethyl-4-phenyl-4-piperidols	Number of fractions taken	Total volume of solution emerging from column (ml)	Amount of piperidol isolated (g)	Isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol isolated
$\alpha + \beta$	17	85	—	β α
	23	115	0.6	
	27	135	0.73	
	2	10	Traces	
	2	10	—	
$\alpha + \gamma$	14	70	—	γ α
	22	110	0.7	
	27	135	0.7	
	2	10	Traces	
	2	10	—	
$\beta + \gamma$	14	70	—	γ Mixture of β and γ β
	17	85	0.48	
	13	65	0.4	
	13	65	0.47	
	4	20	Traces	

Footnote: The column was 50 cm in height and 1.5 cm in diameter. The alumina weighed 69 g. The solvent was chloroform. The starting mixture consisted of 0.5-g portions of each isomeric piperidol. The volume of the fractions collected was 5 ml.

added 15.5 ml of propionyl chloride with vigorous stirring. The mixture was kept for 2 days at room temperature and then heated for 3.5 hr with the benzene boiling. The precipitate (1.3 g) of the hydrochloride of the starting α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol was collected. It had m.p. 230-231° (from anhydrous alcohol). The benzene and excess propionyl chloride were removed in vacuum. The residue was washed with absolute ether (trituration of the precipitate with ether) and then dissolved in acetone. Since it was impossible to induce crystallization (α -promedol is very soluble in acetone), anhydrous benzene was added to the solution. Cooling produced 6.7 g of a precipitate with m.p. 78-123°, which was recrystallized from benzene. The crystals thus isolated melted at 151-153°. Heating the precipitate in absolute ether yielded the hydrochloride of the propionate of the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (α -promedol) with m.p. 153-154° (this sample of α -promedol was examined pharmacologically).

TABLE 3

Isomeric 1,2,5-tri- methyl-4- phenyl-4- piperidols	Number of fractions taken	Total volume of solution emerging from col. (ml)	Amount of piperidol isolated (g)	Isomer of 1,2,5-trimethyl- 4-phenyl-4- piperidol isolated
α, β, γ	18	90	—	γ Mixture β and γ α —
	10	50	0.3	
	18	90	0.6	
	21	210	0.45	
	2	10	Traces	
	2	10	—	

Footnote: The column was 50 cm in height and 1.5 cm in diameter. The alumina weighed 69 g. The solvent was chloroform. The starting mixture consisted of 0.5-g portions of each isomeric piperidol. The volume of the fractions collected was 5 ml.

Found %: Cl 11.31, 11.49; N 4.57, 4.41. $C_{17}H_{25}O_2NCl$. Calculated %: Cl 11.39; N 4.49.

Hydrolysis of the propionate of the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (hydrochloride with m.p. 153-154°) with a 15% solution of potassium hydroxide in alcohol gave a quantitative yield of the α -isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol with m.p. 106-107°.

SUMMARY

1. Some considerations are presented on the structure of the α - and γ -isomers of 1,2,5-trimethyl-4-phenyl-4-piperidol, of which α -promedol and promedol are derivatives.
2. The separation of the stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols by chromatography on alumina was studied.
3. A method of isolating α -promedol (m.p. 153-154°) is described.

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AMINATION OF HETEROCYCLIC COMPOUNDS CONTAINING AN IMIDAZOLE RING

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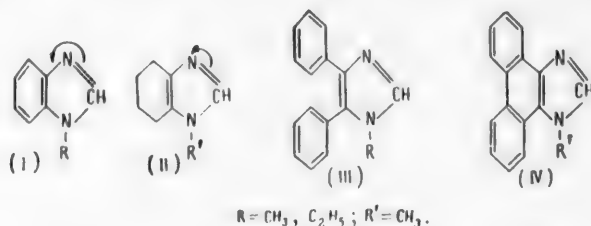
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It was shown previously that in contrast to benzimidazole itself, N-alkyl substituted benzimidazoles (I) are aminated by sodamide to form 2-amino derivatives [1]. 1-Ethylbenzimidazole is also aminated readily. It seemed interesting to determine whether N-substituted derivatives of other heterocycles containing an imidazole ring (apart from benzimidazole) would undergo this reaction. For this purpose we treated 1-methyltetrahydrobenzimidazole (II), 1-methyl- and 1-ethyl-4,5-diphenylimidazole (III), and 1-methylphenanthrimidazole (IV) with sodamide. The experiments were carried out under the conditions for amination of benzimidazole and also at a higher temperature (180-190°).

No liberation of hydrogen was observed in any case; the starting compound was recovered from the reaction mixture in 80-90% yield.



Thus, the only heterocyclic systems out of those which we studied that are capable of reacting with sodamide are derivatives of benzimidazole, i.e., compounds in which the imidazole ring is influenced by the benzene nucleus condensed with it. It is evident that as a result of the displacement of electron density from the imidazole to the benzene nucleus, there arises on the carbon atom in position 2 a very high partial positive charge, which determines the possibility of nucleophilic substitution at the CH group. These ideas are confirmed by quantum mechanical calculations [2].

In N-methyltetrahydrobenzimidazole, the electron density in position 2 is reduced much less than in benzimidazole (I), as polarization in the $-N=CH$ group is produced only by the hetero atom. There is approximately the same electron density distribution in compounds (III) and (IV); in the imidazole derivative (III) the benzene nuclei apparently are not conjugated with the imidazole ring, while in phenanthrimidazole (IV) the effect of the middle nucleus, whose aromaticity is low, as in phenanthrene itself, naturally cannot have an effect equivalent to that of the benzene nucleus in benzimidazole.

The behavior of the unalkylated heterocycles (I)-(IV) ($R = R' = H$) toward diazo compounds confirms the hypotheses put forward; while tetrahydrobenzimidazole, 4,5-diphenylimidazole, and phenanthrimidazole, like 4,5-dimethylimidazole [3], readily couple in position 2 in an alkaline medium to form azo compounds, benzimidazole does not react with diazo compounds. Consequently the displacement of electron density from the imidazole to the benzene nucleus in benzimidazole is so great that even in the anion form it does not undergo the given electrophilic substitution.

The effect of the imidazole ring on the benzene ring in the benzimidazole series was characterized in the work of L. S. Éfros [4]. Our observations show that, as might have been expected, the effect of the benzene on the imidazole nucleus is also very great in these compounds.

Azo Compounds Containing an Imidazole Ring

Starting materials		Color of azo compound	Melting point	Empirical formula	% N		Color of solution of azo compound in concentrated sulfuric acid
azo component	diazo component				found	calculated	
4,5-Diphenylimidazole	Aniline p-Chloroaniline Benzidine	Yellow Yellow Red	217-218° 216 283-284	$C_{21}H_{16}N_4$ $C_{21}H_{15}N_4Cl$ $C_{42}H_{30}N_8$	17.05 15.80 17.12	17.26 15.61 17.33	Bright blue
Phenanthrimidazole	p-Chloroaniline Benzidine	Orange Violet	Did not melt up to 300° The same	$C_{21}H_{13}N_4Cl$ $C_{42}H_{26}N_8$	15.89 17.28	15.67 17.45	
Tetrahydrobenzimidazole	p-Chloroaniline	Light yellow	193-194°	$C_{13}H_{13}N_4Cl$	21.17	21.49	Crimson

EXPERIMENTAL

1-Ethylbenzimidazole was obtained by boiling (2 hr) an alcohol solution of benzimidazole, ethyl iodide (2 moles), and potassium hydroxide (2 moles). The potassium iodide was separated, the alcohol removed, the residue dissolved in chloroform, and the chloroform solution washed with alkali. The product had b.p. 159-160° (11 mm). The properties of the base and its picrate corresponded to literature data [5]. The yield was 40%.

2-Amino-1-ethylbenzimidazole. The amination of 1-ethylbenzimidazole with sodamide was carried out in dimethylaniline at 120-125° according to [1b]. The yield was 58%. The colorless, needlelike crystals had m.p. 158° (from benzene) and were readily soluble in alcohol and water.

Found %: N 26.21, 26.41. $C_9H_{11}N_3$. Calculated %: N 26.07.

The picrate formed yellow needles with m.p. 284° (from alcohol).

Found %: N 21.57. $C_9H_{11}N_3 \cdot C_6H_3O_7N_3$. Calculated %: N 21.53.

Hydrochloride. The snow-white, needlelike crystals had m.p. 100-103° (from alcohol with ether) and contained 1 molecule of water. The anhydrous salt melted at 178-179° (drying at 90-100°).

Found %: Cl 17.77, 17.97. $C_9H_{11}N_3 \cdot HCl$. Calculated %: Cl 17.93.

1-Methyltetrahydrobenzimidazole was obtained by heating tetrahydrobenzimidazole [6] with dimethyl sulfate on a water bath for 10 min. The yield was 53%.

The picrate had m.p. 215°. Literature data [7]: m.p. 214-216°.

4,5-Diphenylimidazole. The variant of the known method [8, 12] that we developed for the synthesis of 4,5-diphenylimidazole is simpler and more convenient than other preparation methods [9]. To a solution of 21 g of benzil in 450 ml of methanol* at 5-10° was added 40 ml of formalin (d 1.08) and a stream of ammonia passed in for 2 hr with vigorous mechanical stirring. The colorless precipitate of by-product was removed by filtration and the filtrate heated to 40° and diluted with a 2-fold amount of warm water. After 5-6 hr, the crystals of 4,5-diphenylimidazole were collected and washed with water. The yield was 15.3 g (73%). The lustrous needles (from a mixture of alcohol and benzene) had m.p. 231-232°; literature data: m.p. 231° [9].

1-Methyl-4,5-diphenylimidazole. 4,5-Diphenylimidazole was heated with dimethyl sulfate on a water bath for 20 min and the reaction product purified by sublimation at 10-12 mm. The

* Complete solution of the benzil was unnecessary as the solid dissolved completely when ammonia was introduced.

yield was 54%. The lustrous platelets had m.p. 158° (from aqueous alcohol); literature data: m.p. 147° [10] and 158° [11]. The compound was not aminated when heated with sodamide in diethylaniline at 210°.

1-Ethyl-4,5-diphenylimidazole. 4,5-Diphenylimidazole was ethylated under the conditions used for the synthesis of 1-ethylbenzimidazole. The product had b.p. 221-223° (8 mm). The yield was 69%. The needlelike crystals had m.p. 95° (from aqueous alcohol or ether); literature data: m.p. 94-95° [12].

1-Methylphenanthrimidazole was synthesized previously by the reaction of phenanthrenequinone [13] and 10-amino-9-phenanthrol hydrochloride [14] with methylamine and had m.p. 185-186° [13] and 195° (corr.) [14]. We prepared it by methylation of phenanthrimidazole [15] with dimethyl sulfate (1 mole) and purified it by vacuum sublimation. The yield was 50%. The lustrous white platelets had m.p. 190-191° (from aqueous alcohol).

Found %: N 12.08, 12.21. $C_{16}H_{12}N_2$. Calculated %: N 12.06.

Azo coupling of compounds containing an imidazole ring. To an alcohol solution of the heterocyclic compound at 0° were added a diazo solution obtained from an equimolecular amount of the amine (0.5 mole of benzidine) and a 10% solution of sodium carbonate. The precipitated azo compound was collected, washed with water, recrystallized from aqueous alcohol, and dried in vacuum (20 mm) at 60-70°. The yield was almost quantitative (see table).

SUMMARY

1. It was established that in contrast to 1-alkylbenzimidazoles, N-alkyl derivatives of tetrahydrobenzimidazole, 4,5-diphenylimidazole, and phenanthrimidazole are not aminated by sodamide.

2. The behavior of the heterocyclic systems (I)-(IV), containing an imidazole ring with an unsubstituted NH group, toward electrophilic reagents was compared with that of the N-alkyl derivatives of these heterocycles toward nucleophilic reagents.

3. 1-Ethylbenzimidazole was aminated.

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SYNTHESIS OF 2-BENZHYDRYLINDAN-1,3-DIONE AND ITS 2-AMINO DERIVATIVES

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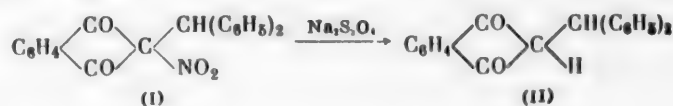
Original article submitted January 31, 1960

We showed [1-5] that 2-amino derivatives of 2-phenyl- and 2-anisylindan-1,3-diones have valuable physiological properties and are similar to barbiturates [6]. By synthesizing 2-amino derivatives of 2-benzhydrylindan-1,3-dione, we expected to obtain new physiologically active derivatives of indan-1,3-dione, as the introduction of a benzhydryl group into organic compounds is known to make them physiologically active [7-11]. Some benzhydryl derivatives have found application in medicine [12].

We decided to use the reaction of 2-halo-2-benzhydrylindan-1,3-dione with amines for the preparation of 2-amino derivatives of 2-benzhydrylindan-1,3-dione. In this connection it was necessary to develop a convenient method of preparing 2-benzhydrylindan-1,3-dione itself and its bromination product.

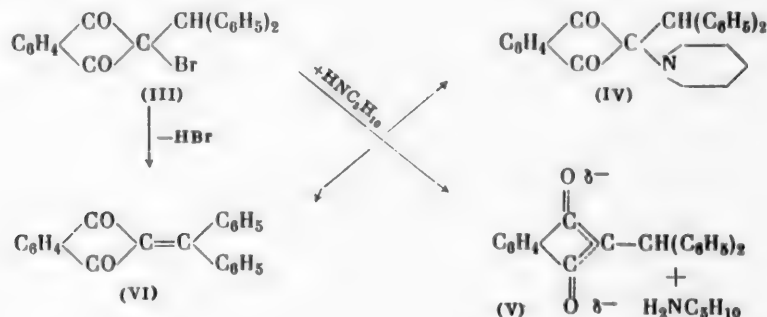
It was established previously that 2-nitroindan-1,3-dione condenses readily with benzhydrol [13] to form 2-nitro-2-benzhydrylindan-1,3-dione (I). In addition, it was shown [14] that the reduction of 2-nitro-2-benzhydrylindan-1,3-dione with tin and hydrochloric acid in alcohol gives 2-benzhydrylindan-1,3-dione (II) and 2-amino-2-benzhydrylindan-1,3-dione. Both products were obtained in low yields. Stannous chloride in hydrochloric acid also reduces 2-nitro-2-phenylindan-1,3-dione to 2-phenylindan-1,3-dione [15].

We established that sodium hydrosulfite in alcohol converts 2-nitro-2-benzhydrylindan-1,3-dione to 2-benzhydrylindan-1,3-dione in good yield (74-78%).

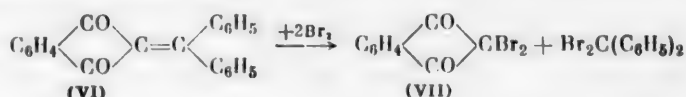


Bromination of the latter with bromine in glacial acetic acid yielded 2-bromo-2-benzhydrylindan-1,3-dione (III), which was treated with piperidine, diethylamine, ethylamine, and ammonia. It was found that hardly any of the expected amino compound was formed, and the reaction was more complex and similar to the reaction of 2-bromo-2-p-nitrophenylindan-1,3-dione with amines [16].

The reaction of 2-bromo-2-benzhydrylindan-1,3-dione (III) with piperidine proceeded in three directions with the formation of the products (IV), (V), and (VI).



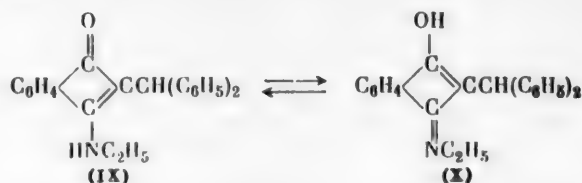
The main reaction product was the piperidine salt of 2-benzhydrylindan-1,3-dione (V). There was partial elimination of hydrogen bromide with the formation of 2-diphenylmethylenelindan-1,3-dione (VI), which has not been described in the literature. It did not add bromine in the cold in benzene as is often observed with ethylene derivatives in which the double bond is surrounded by electrophilic groups [17]. When the product (VI) was boiled with excess bromine in glacial acetic acid, the molecule was cleaved at the ethylene bond as occurs with *cis*-bis-bindonylene [18] and arylidenebindones [19].



The expected 2-piperidino-2-benzhydrylindan-1,3-dione (IV) was formed only in insignificant amounts. Its formation was indicated only by the infrared spectrum of the incompletely purified piperidine salt of 2-benzhydrylindan-1,3-dione.

2-Bromo-2-benzhydrylindan-1,3-dione reacted with diethylamine with more difficulty than with piperidine. In this case a small amount of the diethylamine salt of 2-benzhydrylindan-1,3-dione was formed, and part of the starting bromo compound was recovered. Under more drastic conditions, the salt was largely formed and the starting bromo compound was recovered only in very small amounts together with the unsaturated compound (VI).

In the reaction of 2-bromo-2-benzhydrylindan-1,3-dione with ethylamine, the only reaction product isolated was the ethylimine of 2-benzhydrylindan-1,3-dione, which may exist in the tautomeric forms (IX) and (X).



The same imine was obtained if excess ethylamine was added to a suspension of 2-benzhydrylindan-1,3-dione in alcohol. It has been reported in the literature [20] that the imino derivatives is formed readily by the reaction of 2-bromo-2-benzhydrylindan-1,3-dione with β -naphthylamine.

2-Bromo-2-benzhydrylindan-1,3-dione reacted with ammonia with difficulty and formed only the ammonium salt of 2-benzhydrylindan-1,3-dione.

From the experimental data obtained it follows that the bromine atom in 2-bromo-2-benzhydrylindan-1,3-dione is less reactive than in 2-bromo-2-phenyl-, 2-bromo-2-anisyl-, 2-bromo-2-p-nitrophenyl-, and 2-bromo-2-methylindandiones [20]. The reduction in the reactivity of the bromine atom in 2-bromo-2-benzhydrylindan-1,2-dione is apparently connected with the steric hindrance of the benzhydryl group to the nucleophilic attack of the amine molecule on position 2.

Infrared absorption spectra were plotted on suspensions of the substances synthesized in paraffin oil and solutions of 1,2-dichloroethane (see table). The spectra were plotted on an IKS-12.

2-Benzhydrylindan-1,3-dione, like other 2-substituted indan-1,3-diones, is characterized by two valence vibrations of the carbonyl groups at 1702 and 1736 cm^{-1} [21]. 2-Benzhydrylindan-1,3-dione apparently exists in the diketo form in the solid state. The 2-nitro and 2-bromo derivatives give somewhat high frequencies for the vibrations of the carbonyl groups at 1718 and 1754 cm^{-1} , and 1713 and 1742 cm^{-1} , respectively, as is normally observed with α -bromo and α -nitro ketones [22, 25, 26].

The 2-diphenylmethylenelindan-1,3-dione (VI), which was obtained for the first time, was also characterized by two absorption maxima of the carbonyl groups at 1683 and 1719 cm^{-1} . The reduction in the vibration frequencies of the carbonyl groups indicates the presence of a conjugated system in the molecule [23]. The conjugated double bond $\text{C}=\text{C}$ absorbs at 1631 cm^{-1} . This frequency did not change in dichloroethane solution. 2-Benzalindan-1,3-dione, which is structurally similar, absorbs analogously. It should be noted that high values are given in the literature [24] for the frequencies of the carbonyl groups.

Most Characteristic Frequencies of Compounds Studied

Compound	Medium	ν cm ⁻¹ (absorption intensity in %)				
		C=O	C=C	aromatic ring	NO ₂ (asym.)	C=N or C=O
2-Benzhydrylindan-1,3-dione	A	1702 (98), 1736 (70)	—	1589 (52)	—	—
2-Nitro-2-benzhydrylindan-1,3-dione	A	1718 (98), 1754 (87)	—	1590 (81)	1545 (100)	—
2-Bromo-2-benzhydrylindan-1,3-dione	A	1713 (100), 1742 (95)	—	1592 (100)	—	—
2-Diphenylmethyleneindan-1,3-dione	A	1683 (95), 1719 (59)	1631 (60)	1570 (81), 1596 (71)	—	—
	B	1686 (95), 1720 (42)	1631 (37)	1570 (79), 1600 (59)	—	—
2-Benzalindan-1,3-dione	A	1684, 1724	1618	1592	—	—
	A**	1696, 1737	1620	1575, 1600	—	—
Diethylamine salt of 2-benzhydrylindan-1,3-dione	A	1514 (87)		1614 (85)	—	—
Piperidine salt of 2-benzhydrylindan-1,3-dione	A***	a) 1699 (56), 1732 (42)	1535 (95)	1604 (80)	—	—
		b) — —	1535 (95)	1604 (79)	—	—
Ethylamine of 2-benzhydrylindan-1,3-dione	A		1519 (92)	1615 (58)	—	1636 (56)

* A — suspension in paraffin oil; B — solution in 1,2-dichloroethane.

** Literature data [24].

*** a) After one recrystallization; b) carefully purified product.

The diethylamine salt of the enol form of 2-benzhydrylindan-1,3-dione is characterized by an intense, broad absorption maximum at 1514 cm⁻¹, which is probably connected with the absorption of the equalized system of double bonds C=O and C=C of the enolate anion (V).

This maximum appears at 1535 cm⁻¹ with the piperidine salt. If this salt was not purified adequately (after one recrystallization), the spectrum showed absorption maxima of average intensity at 1699 and 1732 cm⁻¹, which indicated the presence of the 2-piperidino derivative (IV). These absorption maxima disappeared with recrystallization.

The product from the reaction of 2-bromo-2-benzhydrylindan-1,3-dione with ethylamine was characterized by absorption in the double bond region at 1636, 1615, and 1519 cm⁻¹. While the frequency of 1519 cm⁻¹ could be assigned to the absorption of the strongly equalized C=C bond in the five-membered ring (IX) or (X) and the frequency of 1615 cm⁻¹ to the absorption of the aromatic ring, the nature of the absorption band at 1636 cm⁻¹ has not been determined. This absorption maximum may be assigned to absorption of the C=O in the enamino ketone (IX) or to the absorption of the C=N bond in the imino enol (X) with equal probability [27]. No absorption of OH or NH groups was observed. The compound is apparently strongly associated in the solid state. The structure of the product studied cannot be determined unequivocally from the spectroscopic data we obtained.

EXPERIMENTAL

2-Benzhydrylindan-1,3-dione (II). A mixture of 12.5 g of 2-nitro-2-benzhydrylindan-1,3-dione, 250 ml of alcohol, and 25 g of sodium hydrosulfite was boiled for 5 hr. The solution gradually became orange. The unreacted hydrosulfite was removed by filtration, about 250 ml of alcohol distilled from the filtrate, and the residue diluted with hydrochloric acid (1:1). An oily substance precipitated and this gradually solidified. Recrystallization from alcohol yielded 8.1-8.5 g (74-78%) of 2-benzhydrylindan-1,3-dione. The colorless crystals had m.p. 127-128°. The

melting point of a mixture with 2-benzhydrylindan-1,3-dione obtained by reduction of 2-nitro-2-benzhydrylindan-1,3-dione with tin and hydrochloric acid [14] was not depressed.

2-Bromo-2-benzhydrylindan-1,3-dione (III). A solution of 2.1 ml of bromine in 10 ml of glacial acetic acid was added dropwise to a warm ($\sim 60^\circ$) solution of 12 g of 2-benzhydrylindan-1,3-dione in 100 ml of glacial acetic acid. Hydrogen bromide was evolved vigorously, and the bromination product began to crystallize from the still-warm solution. The next day the precipitate was collected and recrystallized from glacial acetic acid. The yield was 13 g (87%). The colorless crystals had m.p. $147-148^\circ$.

Found %: Br 20.18. $C_{22}H_{18}O_2Br$. Calculated %: Br 20.42.

Reaction of 2-bromo-2-benzhydrylindan-1,3-dione with amines. 1) **With piperidine.** A solution of 1.2 ml of piperidine in 5 ml of absolute ether was added dropwise to a solution of 2 g of 2-bromo-2-benzhydrylindan-1,3-dione in 20 ml of a mixture of absolute ether and anhydrous dioxane (1:1). The solution became orange-yellow and a colorless crystalline precipitate of piperidine hydrobromide appeared. The solution was left at room temperature for 2 days; the solution gradually became red-orange and orange crystals separated. The reaction mixture was boiled for half an hour, cooled, filtered, and the precipitate washed first with ether and then with water (for the removal of piperidine hydrobromide). The orange precipitate remaining on the filter was recrystallized from ethanol with ether added. We obtained 0.7 g (34.2%) of the piperidine salt of 2-benzhydrylindan-1,3-dione (V). The yellow-orange crystals had m.p. 202° . They were readily soluble in water, alcohol, and dioxane and insoluble in ether. Acidification of the aqueous solutions yielded 2-benzhydrylindan-1,3-dione.

Found %: N 3.42. $C_{27}H_{27}O_2N$. Calculated %: N 3.53.

The ether-dioxane filtrate was evaporated in vacuum. The oily residue was washed with water, dissolved in ether, dried with sodium sulfate, and evaporated in vacuum. The yellow, resinous residue was washed with 80% methanol. We obtained 0.5 g (31.6%) of 2-diphenylmethyleindan-1,3-dione (VI) with m.p. $\sim 163^\circ$. Recrystallization from ethanol gave 0.4 g (25.3%) of yellow crystals with m.p. $165-167^\circ$. The substance was readily soluble in ether, benzene, 1,2-dichloroethane, and dioxane and sparingly soluble in methanol and ethanol.

Found %: C 85.33; H 4.64. $C_{22}H_{14}O_2$. Calculated %: C 85.14; H 4.55.

2) **With diethylamine.** a) To a solution of 1.3 g of 2-bromo-2-benzhydrylindan-1,3-dione in 20 ml of a mixture of anhydrous dioxane and absolute ether was added 0.75 ml of diethylamine in 10 ml of absolute ether; the rest of the procedure was as in the reaction with piperidine. We obtained 0.35 g of the diethylamine salt of 2-benzhydrylindan-1,3-dione. The red-orange crystals had m.p. $181-183^\circ$ (decomp., from alcohol with ether added). Evaporation of the ether-dioxane filtrate in vacuum gave a dark residue, recrystallization of which from alcohol gave 0.8 g of the starting 2-bromo-2-benzhydrylindan-1,3-dione with m.p. $146-148^\circ$.

b) To a solution of 2 g of 2-bromo-2-benzhydrylindan-1,3-dione in 20 ml of a mixture of anhydrous dioxane and absolute ether was added a solution of 2 ml of diethylamine in 10 ml of absolute ether. On the next day the reaction mixture was boiled for 3 hr. The precipitate was collected from the cooled mixture and washed with water. There remained 1 g of the diethylamine salt of 2-benzhydrylindan-1,3-dione. The red-orange crystals had m.p. $181-183^\circ$ (decomp.). They were readily soluble in water, alcohol, and dioxane and insoluble in ether. Acidification of aqueous solutions liberated 2-benzhydrylindan-1,3-dione.

Found %: N 3.43. $C_{26}H_{27}O_2N$. Calculated %: N 3.63.

It was impossible to isolate individual substances from the ether-dioxane solutions.

3) **With ethylamine.** To a solution of 2 g of 2-bromo-2-benzhydrylindan-1,3-dione in 20 ml of a mixture of anhydrous dioxane and absolute ether (1:1) was added a solution of 1.5 ml of ethylamine in 10 ml of absolute ether. The solution became red and deposited a red oil, which did not solidify on standing. After 2 days, the mixture was evaporated in vacuum, the dark oily residue washed with water and then ether, and the residual red-orange substance (0.85 g) recrystallized from alcohol with ether added. We obtained 0.6 g of orange crystals of the ethylimine of 2-benzhydrylindan-1,3-dione (IX) or (X) with m.p. 164° . The substance was sparingly soluble in water, dioxane, and alcohol and insoluble in ether and dichloroethane. Dilute hydrochloric acid did not have an immediate effect on the ethylimine of 2-benzhydrylindan-1,3-dione, but gradually cleaved it to 2-benzhydrylindan-1,3-dione.

Found %: N 4.46, 4.30. $C_{24}H_{21}ON$. Calculated %: N 4.13.

4) With ammonia. Dry ammonia was passed for 2 hr into a solution of 2 g of 2-bromo-2-benzhydrylindan-1,3-dione in 10 ml of anhydrous dioxane and then the reaction mixture treated as in the reaction with ethylamine. Crystallization began when the solution was evaporated. The crystals were collected and washed with ether. The residue was found to be ammonium bromide (0.2 g). The ether solution was evaporated in vacuum and the residue washed with water and recrystallized from alcohol. We obtained 0.8 g of the starting 2-bromo-2-benzhydrylindan-1,3-dione with m.p. 146-148°. Acidification of the wash waters yielded a small amount of 2-benzhydrylindan-1,3-dione with m.p. 127°.

Reaction of 2-diphenylmethyleindan-1,3-dione with bromine. a) To a solution of 0.1 g of 2-diphenylmethyleindan-1,3-dione in 2 ml of benzene was added a solution of 0.03 ml of bromine in 2 ml of benzene and the mixture allowed to evaporate slowly. We recovered 0.08 g of the starting substance with m.p. 165-167°.

b) A mixture of 0.1 g of diphenylmethyleindandione, 3 ml of glacial acetic acid, and 0.2 ml of bromine was boiled for half an hour, the excess bromine removed in vacuum, and the residue gradually diluted with water. Colorless crystals of 2,2-dibromoindan-1,3-dione (VII) with m.p. 176° (from glacial acetic acid) precipitated; a mixed melting point with authentic 2,2-dibromoindan-1,3-dione (m.p. 178°) was not depressed.

SUMMARY

Reduction of 2-nitro-2-benzhydrylindan-1,3-dione with sodium hydrosulfite gave a good yield of 2-benzhydrylindan-1,3-dione, and bromination of the latter gave 2-bromo-2-benzhydrylindan-1,3-dione.

The reaction of 2-bromo-2-benzhydrylindan-1,3-dione with amines did not yield 2-amino derivatives. The reaction with piperidine and diethylamine formed mainly the corresponding salts of the enol form of 2-benzhydrylindan-1,3-dione and small amounts of 2-diphenylmethyleindan-1,3-dione, while the ethylimine of 2-benzhydrylindan-1,3-dione was not formed with ethylamine. The reaction with ammonia was slow, and the only product was the ammonium salt of the enol form of 2-benzhydrylindan-1,3-dione.

The low reactivity of the bromine in 2-bromo-2-benzhydrylindan-1,3-dione may be explained by steric hindrance created by the benzhydryl group.

2-Diphenylmethyleindan-1,3-dione was cleaved at the ethylenic bond by bromine in acetic acid to form 2,2-dibromoindan-1,3-dione.

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PREPARATION OF 5-HYDROXY- γ -PYRONE-2-CARBOXYLIC ACID AND 3-HYDROXY- γ -PYRONE

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Comenic acid (5-hydroxy- γ -pyrone-2-carboxylic acid) and 3-hydroxy- γ -pyrone (pyromeconic acid) are obtained by decarboxylation of meconic acid. Syntheses have been described for them, but they are of no preparative value.

A number of authors have described methods of isolating meconic acid in the preparation of opium alkaloids [1-3]. Their drawbacks were reduced to a minimum in the method of one of us [4], but the isolation was quite laborious even in this case.

Comenic acid is obtained by decarboxylation of meconic acid either by dry distillation [5, 6] or by the action of dilute HCl [3] (its formation by boiling meconic acid with water has been reported [5]). Comenic acid was later obtained by a number of authors [7-10] with modified purification methods, namely recrystallization of the sodium, potassium [6], or ammonium salts [2]. Later authors [11-16] have not introduced any substantial modifications.

In the preparation of 3-hydroxy- γ -pyrone from meconic acid, most authors reported dry distillation temperatures of 227-228° [12], 260-315° [17], up to 300° [8], and up to 300° in a stream of CO₂ [18]. The use of a mixture with copper powder gave a yield of up to 45% [19] and dry distillation of meconic acid with copper bronze in vacuum yielded a mixture of comenic acid and 3-hydroxy- γ -pyrone directly from meconates, i.e., the by-product in the preparation of opium alkaloids. This eliminated the difficulties of isolating meconic acid itself.

In the present work we present the most up-to-date methods of preparing comenic acid and 3-hydroxy- γ -pyrone directly from meconates, i.e., the by-product in the preparation of opium alkaloids. This eliminated the difficulties of isolating comenic acid itself.

Comenic acid was previously obtained by this method [20] in the form of snow-white crystals, which could be decarboxylated at 220-230°. It was then found that it largely sublimed, and this was carried out at 210-215° to obtain acid of higher purity. When impurities were present it did not sublime at all (technical comenic acid) or only partly. We characterized comenic acid of higher purity (h.p.) by this property of the acid in combination with analysis and titration data as its decomposition point was not characteristic.

We utilized the high solubility of comenic acid in concentrated sulfuric acid, especially on heating, to free it from impurities, and this was more effective than recrystallization of its salts. In addition, we found a simple and effective method of preparing it directly from meconates, which consisted in boiling meconates with dilute HCl and then evaporating the solution, when the meconic acid was decarboxylated. The reaction product obtained was purified by recrystallization from very dilute HCl.

For the preparation of 3-hydroxy- γ -pyrone directly from meconates, the latter were treated as above, and the comenic acid was converted to the salt without purification and dry distilled.

EXPERIMENTAL

Sublimation temperature of comenic acid. Ground crystals were deposited on a thermometer at the mercury bulb (on the side of the scale). The thermometer was placed in a tube, which was heated at 8° per minute. At 210-215°, the crystals disappeared completely after 10-15 min and part of the sublimate collected on the wall of the tube as lustrous white crystals. A slight dark or colored tarry residue with partial sublimation indicated the presence of impurities. The sublimate collected from several portions of crystals was also sublimed at 210-215°.

Found %: C 46.05; H 2.50. $C_6H_4O_5$. Calculated %: C 46.15; H 2.56.

Comenic acid (h.p.) was prepared from meconates of higher (a) and lower (b) quality. a) To 14 ml of HCl (d 1.19) and 7 ml of water was added 10 g of dry meconates in portions with stirring at 10°. After half an hour, the precipitate was collected and washed with chloroform and iced water. The precipitate was transferred from the filter to 15 ml of dilute HCl (1:1) at 85°. Decarboxylation was complete in 1 hr. The next day, the precipitate was collected, washed with iced water and alcohol, and dissolved in 200 ml of boiling water and 12 ml of HCl (1:1); the solution was filtered with charcoal. On the next day the precipitate was collected and washed with iced water. The weight was 3.0 g. The sublimation temperature was 210-215°; equiv. 156.9, 157.2, M 156.

Found %: C 46.60; H 2.50. $C_6H_4O_5$. Calculated %: C 46.15; H 2.56.

b) A 20-g sample of dry meconates was boiled for 20 min with 80 ml of water and 40 ml of HCl (1:1) (2 moles per mole of meconates, considering them as 100%). After hot filtration of the mixture, the slight residue was washed with 10 ml of hot water and the filtrate boiled for 20 min, filtered with charcoal, boiled again for a further 20 min, and filtered with charcoal. The filtrate was evaporated in a dish on a boiling water bath to 40 ml in about 1 hr. The dark brown mass was poured into 20 ml of water and the solution saturated with salt. On the following day, the precipitate was collected, washed with iced water, and dissolved in 150 ml of boiling water with 9 ml of HCl (1:1). After the solution had been filtered hot with charcoal twice, the precipitate which formed was collected next day and washed with iced water. The weight was 1.75 g (9% on the starting meconates). The sublimation temperature was 210-215°; equiv. 161.4, M 156.

Found %: C 45.70; H 2.41. $C_6H_4O_5$. Calculated %: C 46.15; H 2.56.

Treatment of these meconates according to a necessitated precipitation of the neutral sodium salt of comenic acid with alcohol, acidification with HCl, heating a solution of the liberated comenic acid with H_2SO_4 (d 1.83) at 100° for 1.5 hr, and recrystallization of its acid sodium salt.

3-Hydroxy- γ -pyrone from comenic acid (h.p.). A mixture of 10 g of dry comenic acid and 10 g of copper powder was heated in a stream of CO_2 in a flask with a wide inlet tube sealed on down low and connected to a cooling jacket on a sand bath at 260-280° (240-250° inside the reaction mixture). The sublimate and part of the liquid was recrystallized from chloroform. The weight of the crystals was 3.0 g. The m.p. was 117°. The crystals gave a red color with aqueous and alcohol solutions of $FeCl_3$.

Found %: C 53.67; H 3.72. $C_5H_4O_3$. Calculated %: C 53.57; H 3.57.

3-Hydroxy- γ -pyrone from meconates. a) A mixture of 20 g of dry meconates and 30 ml of H_2SO_4 (d 1.83) was heated on a boiling water bath for 1.5 hr and then poured onto ice. The next day the precipitate was collected and washed with iced water. The precipitate was mixed with 14 g of copper powder and decarboxylated under the conditions of the previous experiment to yield 0.2 g (1.0%) of crystals. The m.p. was 117° (from $CHCl_3$). A mixed melting point with the crystals obtained in the previous experiment was not depressed.

b) A 40-g sample of meconates was dissolved in 160 ml of water and 80 ml of HCl (1:1) as described in the preparation of comenic acid by method b. The dry reaction product after decarboxylation was pyrolyzed. The weight of the crystals was 1.8 g. The m.p. was 117° (from $CHCl_3$). A mixed melting point with the crystals obtained from comenic acid was not depressed.

SUMMARY

1. A method which has not been described in the literature is proposed for the preparation of 5-hydroxy- γ -pyrone-2-carboxylic acid (comenic acid) directly from meconates.
2. A sublimation temperature of 210-215° is suggested as a characteristic of comenic acid of higher purity.
3. A method that has not been described in the literature is proposed for the preparation of 3-hydroxy- γ -pyrone directly from meconates.

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REACTIONS OF SILICON PEROXIDES WITH SOME TERTIARY ALCOHOLS

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In the last three years a series of papers has appeared on a new type of peroxide compound, namely hetero-organic peroxides. Up to now, compounds of the type



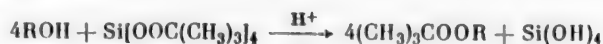
where for (I) El is Cd [1], B [2], Si [3], Ge [4], Sn [5], Pb [6], and P [7] and for (II) El is B, Si, and Ge, have been prepared. The synthesis of heteroorganic peroxide compounds and the investigation of their reactions are of definite theoretical and practical interest. It has been reported [1, 3] that some silicon and boron peroxides produce the polymerization of vinyl compounds.

The large number of reactions of silicon peroxides with different reagents described in the literature [8] includes the reaction of silicon peroxides with tertiary alcohols in the presence of acids. It seemed interesting to us to extend this reaction to some new subjects to study the possibilities of synthesizing unsymmetrical organic peroxides of the type ROOR'. For this purpose we studied the reaction of triphenylcarbinol with tetra(tert-butylperoxy)silane, trimethyl(α-cumylperoxy)silane, and trimethyl(diphenylmethylperoxy)silane and also the reactions of dimethylphenylcarbinol, trimethylcarbinol, and 1-methylcyclohexanol with tetra(tert-butylperoxy)silane. The reaction was effected by treating an acetic acid solution of the tertiary alcohol (in the presence of small amounts of H₂SO₄) with an ether solution of the silicon peroxide. The reaction of triphenylcarbinol with a solution peroxide yielded the corresponding unsymmetrical peroxide of the type ROOR', namely, tert-butyl triphenylmethyl peroxide, α-cumyl triphenylmethyl peroxide, and diphenylmethyl triphenylmethyl peroxide. They were also solids and could be isolated readily. The liquid peroxide tert-butyl 1-methylcyclohexyl peroxide was obtained by the reaction of tetra(tert-butylperoxy)silane with 1-methylcyclohexanol.

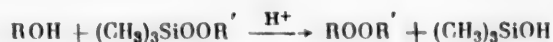
The reactions of tetra(tert-butylperoxy)silane with trimethylcarbinol and dimethylphenylcarbinol proceeded analogously. However, the peroxides ROOR' were not isolated in a pure form in this case.

The reaction of silicon peroxides with tertiary alcohols in the presence of acids is heterolytic and may be represented by the following equations:

for tetra(tert-butylperoxy)silane



for other trimethyl(aralkylperoxy)silanes



(Trimethylsilanol and its dehydration product, hexamethyldisiloxane, were found among the reaction products.)

It should be noted that for the synthesis of the peroxides ROOR' it was necessary to use pure silicon peroxides, though ether solutions of silicon peroxides could be used for this purpose (after removal of pyridine hydrochloride). The reaction was simplified in this way and may be of preparative interest for the synthesis of (CH₃)₃COOR from the readily accessible peroxide tetra(tert-butylperoxy)silane.

EXPERIMENTAL

The silicon peroxides were synthesized by the method reported in the literature [8].

Reaction of tetra(tert-butylperoxy)silane with triphenylcarbinol. To a solution of 1.0 g of triphenylcarbinol in 40 ml of acetic acid and 0.1 ml of sulfuric acid was added 0.4 g of tetra(tert-butylperoxy)silane in 50 ml of ether. The next day the reaction products were poured into water, the silicic acid precipitate removed by filtration, the filtrate neutralized with sodium bicarbonate, and the ether layer washed with 40% KOH solution and dried. After removal of the ether in vacuum, the white precipitate was recrystallized from alcohol. The yield was 1.0 g (78.1%). The m.p. was 70-71.5°. A mixture with authentic tert-butyl triphenylmethyl peroxide melted at 70-71° [9].

Found %: C 83.46; H 7.55. $C_{23}H_{24}O_2$. Calculated %: C 83.13; H 7.23.

Reaction of trimethyl(α -cumylperoxy)silane with triphenylcarbinol. To 2.6 g of triphenylcarbinol in 150 ml of acetic acid were added 0.1 ml of concentrated sulfuric acid and 2.3 g of trimethyl(α -cumylperoxy)silane. The next day the reaction products were treated as described in the previous experiment. We obtained 3.2 g (81%) of the peroxide as colorless crystals, which were insoluble in the usual organic solvents. After being washed with hot alcohol and dried in a vacuum desiccator, the crystals had m.p. 167-169° [9].

Found %: C 85.47; H 6.71. $C_{28}H_{26}O_2$. Calculated %: C 85.28; H 6.55.

Reaction of trimethyl(diphenylmethylperoxy)silane with triphenylcarbinol. To 2.6 g of triphenylcarbinol in 150 ml of acetic acid were added 0.1 ml of sulfuric acid and 2.72 g of trimethyl(diphenylmethylperoxy)silane in 150 ml of ether. The next day the reaction products were neutralized with sodium bicarbonate. From the ether layer, after two distillations, 0.4 g of a substance with b.p. 97-100° and 3.2 g (72%) of a white residue were isolated. The liquid substance contained silicon (benzidine test).

Found %: OH 6.52. $C_9H_{10}OSi$. Calculated %: OH 18.88.

Treatment of the liquid with 12 N sodium hydroxide yielded sodium trimethylsilanolate with m.p. 147-150°. The crystalline residue melted at 88-89° (from ligroin). A mixed melting point with authentic diphenylmethyl triphenylmethyl peroxide [10] was not depressed.

Reaction of tetra(tert-butylperoxy)silane with 1-methylcyclohexanol. To 6.84 g of 1-methylcyclohexanol in 10 ml of acetic acid were added 0.1 ml of concentrated sulfuric acid and 8.7 g of freshly prepared tetra(tert-butylperoxy)silane in 100 ml of absolute ether. After 18 hr, the ether solution was neutralized with sodium bicarbonate, washed twice with 40% potassium hydroxide solution, then water, and dried with $MgSO_4$. After removal of the ether from the residue, 4.8 g (43%) of a fraction was isolated.

B.p. 20-30° (2-2.5 mm), n_D^{20} 1.4372, d_4^{20} 0.892; percent peroxide oxygen 8.51. $C_{11}H_{22}O_2$. Calculated percent peroxide oxygen 8.60.

tert-Butyl 1-methylcyclohexyl peroxide [11] has b.p. 28-29° (2 mm); d_4^{20} 0.881, n_D^{20} 1.4350.

SUMMARY

1. The reaction of tetra(tert-butylperoxy)silane, trimethyl(α -cumylperoxy)silane, and trimethyl(diphenylmethylperoxy)silane with triphenylcarbinol formed peroxides of the type $(C_6H_5)_3COOR$.
2. Tetra(tert-butylperoxy)silane reacts with 1-methylcyclohexanol to form tert-butyl 1-methylcyclohexyl peroxide.

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INVESTIGATION OF PYRAZOLES

XIII. PHOSPHORYLATION OF PYRAZOLES

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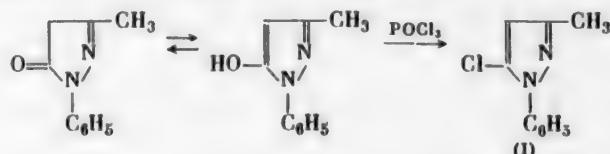
January, 1961

Original article submitted March 1, 1960

In previous articles [1, 2] we have utilized the labile hydrogen in the 4 position of the pyrazole ring to accomplish the thermal benzoylation and benzylation of the ring. In this investigation we have made an attempt at thermal phosphorylation of pyrazoles with the aid of phosphorus oxychloride.

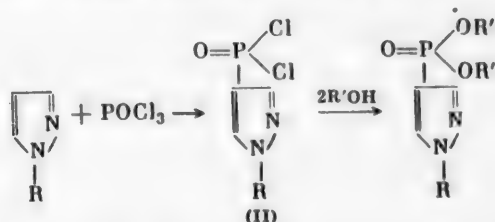
Investigating the conversion of pyrazoles to chloropyrazoles, Michaelis [3] discovered that when phosphorus oxychloride acts on 1-phenyl-3-methylpyrazolone-5, 1-phenyl-3-methyl-5-chloropyrazolyl-4-phosphonic acid is formed in slight amounts. The same compound is obtained when 1-phenyl-3-methyl-5-chloropyrazole is heated with phosphorus oxychloride. The author, however, reported neither the yields nor the detailed method.

Our attempts to repeat these experiments were unsuccessful. When we carried out a reaction between 1-phenyl-3-methylpyrazolone and phosphorus oxychloride at temperatures up to 200°, we obtained only the chloropyrazole (I).



At higher temperatures tarring of the main bulk of the product set in.

1-Phenyl-3-methyl-5-chloropyrazole (I), which has a lowered activity in electrophilic substitution reactions as a result of the decrease in electron density in position 4 of the ring, also did not enter into reaction with phosphorus oxychloride even at 230-240°. Other 1-alkyl and 1-aryl pyrazoles, however, with the usual activity in the 4 position of the ring, reacted with phosphorus oxychloride when the reaction was carried out in sealed tubes (180-190°, 15-25 hours), forming, but not in high yields (15-40%), the acid chlorides of the pyrazolylphosphonic acids (II).



We did not isolate the acid chlorides (II), but treated them immediately with alcohols and converted them to esters, which we identified.

The acid hydrolysis of the esters led to the sirupy pyrazolylphosphonic acids, which are difficult to identify. On alkaline hydrolysis, we observed the splitting out of only one alcohol residue and the formation of an acid ester.

In the case of the slightly active 1,3,5-triphenylpyrazole under very severe conditions (25 hr, 230-240°) we were able to isolate only benzoic acid, which apparently appeared as the product of decomposition of the pyrazole ring.

EXPERIMENTAL

Diethyl ester of (1,3,5-trimethylpyrazolyl-4)-phosphonic acid. In a 60-ml ampoule of good molybdenum glass we heated a mixture of 5.5 g of 1,3,5-trimethylpyrazole and 15.4 g of phosphorus oxychloride at 185-195° for 12 hours. The reaction mass was decomposed with 25 ml of anhydrous alcohol. After the excess alcohol had been distilled off in vacuum the residue was carefully decomposed, with cooling, by 40 ml of concentrated sodium hydroxide solution. The reaction mass was extracted with benzene and the benzene extract was distilled in vacuum. Five and one tenth grams (40.6%) of unpurified ester was obtained with b.p. 165-200° (35 mm). For purification, the compound was distilled twice in vacuum. It did not give a picrate.

B.p. 173-176° (13 mm), n_D^{20} 1.4790, d_4^{20} 1.1255.

Found %: C 48.41, 48.35; H 8.17, 8.12; N 11.78, 11.76; P 11.92, 11.88. $C_{10}H_{19}O_3N_2P$. Calculated %: C 48.76; H 7.78; N 11.41; P 12.38.

The rest of the esters were prepared and purified in a similar way.

Dipropyl ester of (1,3,5-trimethylpyrazolyl-4)-phosphonic acid. Yield 31%.

B.p. 198-200° (18 mm), n_D^{20} 1.4784, d_4^{20} 1.0840.

Found %: C 52.73, 52.63; H 8.93, 8.84; N 10.46, 10.41; P 11.37, 11.26. $C_{12}H_{23}O_3N_2P$. Calculated %: C 52.51; H 8.46; N 10.25; P 11.28.

Dibutyl ester of (1,3,5-trimethylpyrazolyl-4)-phosphonic acid. Yield 44%.

B.p. 212-214° (18 mm), n_D^{20} 1.4768, d_4^{20} 1.0621.

Found %: C 55.90, 55.80; H 9.29, 9.27; P 10.54, 10.44. $C_{14}H_{27}O_3N_2P$. Calculated %: C 55.60; H 9.01; P 10.23.

Dibutyl ester of (1-phenyl-3,5-dimethylpyrazolyl-4)-phosphonic acid. Prepared from 1-phenyl-3,5-dimethylpyrazole in 19% yield.

B.p. 253-254° (17 mm), n_D^{20} 1.5190, d_4^{20} 1.0834.

Found %: C 62.75, 62.45; H 8.39, 8.36; P 8.28, 8.25. $C_{19}H_{25}O_3N_2P$. Calculated %: C 62.41; H 8.29; P 8.44.

Dibutyl ester of (1-phenylpyrazolyl-4)-phosphonic acid. Prepared from 1-phenylpyrazole in 14% yield.

B.p. 263-265° (20 mm), n_D^{20} 1.5215, d_4^{20} 1.0851.

Found %: C 60.38, 60.21; H 8.06, 8.04; P 9.39, 9.25. $C_{17}H_{25}O_3N_2P$. Calculated %: C 60.49; H 7.78; P 9.18.

Monobutyl ester of (1-phenylpyrazolyl-4)-phosphonic acid. Three grams of the dibutyl ester of (1-phenylpyrazolyl-4)-phosphonic acid was dissolved in a mixture of 1 g of potassium hydroxide in 25 ml of propyl alcohol and refluxed for 1.5 hours. During heating a precipitate separated out, which apparently was the sodium salt of the acid. Then the propyl alcohol was distilled off and the residue was treated with 30 ml of 5 N hydrochloric acid. After a day the oil that had separated out crystallized. After crystallization from petroleum ether, 1.8 g of the monobutyl ester was obtained with m.p. 70-72°.

Found %: C 56.82, 56.76; H 6.38, 6.26; P 11.16, 10.95. $C_{13}H_{17}O_3N_2$. Calculated %: C 56.71; H 6.12; P 11.05.

Reaction of 1,3,5-triphenylpyrazole with phosphorus oxychloride. A mixture of 14.8 g of 1,3,5-triphenylpyrazole and 9 ml of phosphorus oxychloride was heated in an autoclave to 210-220° for 25 hours. The reaction mass was treated with 100 ml of anhydrous methanol, boiled with 2 g of activated carbon, and filtered. The filtrate was mixed with 100 ml of concentrated hydrochloric acid and heated at boiling for 15 hours, with the addition of more concentrated hydrochloric acid as the volume of the solution decreased. Then the solution was evaporated to 80 ml and cooled.

One and six tenths grams of benzoic acid was obtained with m.p. 120.5°.

Attempt to synthesis 1-phenyl-3-methyl-5-chloro-4-phosphonic acid. The reaction between 1-phenyl-3-methyl-5-chloropyrazole and phosphorus oxychloride (190-200°) did not go. At 240-250° and 25-hour heating, complete tarring set in and the starting pyrazole could not be separated. When the reaction was carried out between

1-phenyl-3-methylpyrazolone-5 and phosphorus oxychloride at 210-220° for 10 hours, only 1-phenyl-3-methyl-5-chloropyrazole was isolated.

SUMMARY

It has been shown that pyrazoles with a free 4 position in the ring and not containing electron-acceptor substituents in the ring form the acid chlorides of pyrazolyl-4-phosphonic acids when heated with phosphorus oxychloride.

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CONDENSATION OF CYCLOPENTADIENE WITH ALIPHATIC DIENES

III. ISOMERIZATION OF 2-VINYL- AND 2-ISOPROPENYLBICYCLO[2.2.1]HEPTENE-5 TO THE 4,9,7,8-TETRAHYDROINDENE SYSTEM

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January, 1961

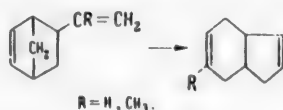
Original article submitted February 21, 1960

It is well known that derivatives of bicyclo[2.2.1]heptane and compounds close to them in structure easily undergo various rearrangements and isomerizations. Thus, there are very numerous reactions which are accompanied by rearrangement of bicyclo[2.2.1]heptene to nortricyclene, which take place on bromination [1] or the addition of various compounds to bicyclo[2.2.1]heptadiene [2] or bicyclo[2.2.1]heptene [3], on solvolysis [4], or in photochemical reactions [5]. Hydration of derivatives of bicyclo[2.2.1]heptene usually is accompanied by Wagner-Meerwein rearrangement [6] or isomerization of the endo isomers to the corresponding exo isomers [7].

A very interesting example of thermal conversion is the transition of the endo isomers to the corresponding exo isomers. It is well known that if the adduct of cyclopentadiene with maleic anhydride, which has an endo configuration, is heated to 180-190°, the corresponding adduct having the exo configuration is formed. This isomerization takes place apparently not by way of the decomposition of the adduct to the starting components, cyclopentadiene and maleic anhydride, and their subsequent reaction, but by way of the formation of a nortricyclene compound, which then undergoes rupture of the C-C bond, or by way of incomplete dissociation of the adduct and recombination of the reaction complex [8-10].

In recent years the thermal isomerization of bicycloheptadiene to cycloheptatriene, which takes place at ~400°, has been discovered and studied [11]; at a higher temperature the isomerization of bicycloheptadiene is directed mainly in the direction of the formation of toluene. Woods [11] suggested that the isomerization of bicycloheptadiene proceeds through the rupture of the C-C bond in the endomethylene bridge. When 1,2,3,4,7,7-hexachlorobicyclo[2.2.1]heptadiene-2,5, is heated to 180° it is isomerized to hexachlorotoluene [12].

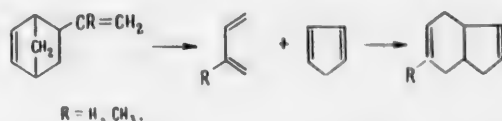
A study of the thermal stability of 2-vinylbicyclo[2.2.1]heptene-5 [13] and 2-isopropenylbicyclo[2.2.1]heptene-5 [14] prepared by us has shown that they have the specific property of easily isomerizing on heating to 4,9,7,8-tetrahydroindene [15] or 5-methyl-4,9,7,8-tetrahydroindene, respectively.



The isomerization of 2-vinylbicyclo[2.2.1]heptene-5 to tetrahydroindene starts at 150°, but proceeds slowly at this temperature. Thus, when the vinylbicycloheptene was heated in a sealed tube at 150° for 12 hours, 7% of tetrahydroindene was formed. With an increase in the time of heating, the yield of tetrahydroindene increases proportionately — when vinylbicycloheptene was refluxed in a flask at 150° for 88 hours, 46-48% of tetrahydroindene was formed. At a higher temperature (300°) the isomerization of vinyl- and isopropenylbicycloheptene proceeds rapidly, but when it is carried out in a circulating apparatus it is accompanied by partial breakdown of the starting hydrocarbon in the manner of a retrodiene synthesis. Thus, when vinylbicycloheptene was passed through a tube heated to 300°, 50% of it isomerized to tetrahydroindene, 48.5% decomposed to cyclopentadiene and butadiene, and 1.5% of the vinylbicycloheptene was unchanged. When isopropenylbicycloheptene was passed through a tube at 300°, 69% isomerized to 5-methyltetrahydroindene and 30% decomposed to cyclopentadiene and isoprene; 1% of the isopropenylbicycloheptene was recovered.

The isomerization of vinyl- and isopropenylbicycloheptene precisely to tetrahydroindene and 5-methyltetrahydroindene, respectively, was demonstrated by comparison of the physical properties of the compounds obtained with the properties of these compounds obtained by us previously by the condensation of cyclopentadiene with butadiene and isoprene [13, 14] and also by the fact that on dehydrogenation the tetrahydroindene formed indane and the isopropenylbicycloheptene formed 5-methylindane.

It was natural to suppose that the isomerization of vinyl- and isopropenylbicycloheptene to tetrahydroindene and methyltetrahydroindene, respectively, might proceed through a stage of decomposition to cyclopentadiene and butadiene (or isoprene) with a subsequent reaction in which the butadiene or isoprene plays the role of the diene.

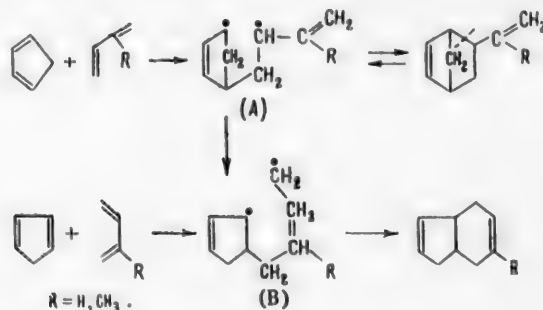


However, special experiments on the condensation of cyclopentadiene with butadiene and isoprene, respectively, by passing them through a tube at 300° (i.e., under the conditions where isomerization occurs) showed that in this case neither dimerization nor copolymerization of the above-mentioned diene hydrocarbons took place. If the isomerization proceeded through a stage of decomposition to cyclopentadiene and butadiene or isoprene and their subsequent reaction, then, of course, dimers of cyclopentadiene and butadiene should be found in the reaction products along with the codimers, and this did not occur. The fact that isomerization takes place even on simply boiling the vinylbicycloheptene in a flask also argues against the assumption of a preliminary decomposition to the starting components. If in this case cyclopentadiene and butadiene were formed, then the latter (b.p. -4°) under the experimental conditions should partially volatilize. Consequently, the isomerization of vinyl- and isopropenylbicycloheptene to tetrahydroindene does not proceed through a stage of formation of cyclopentadiene and butadiene (or isoprene).

It also could be assumed that the isomerization takes place as a result of rupture of the C-C bond in the endomethylene bridge and closure of a new ring at the expense of the vinyl group and a carbon of the endomethylene bridge. This assumption, however, which seemed entirely probable in the case of vinylbicycloheptene [15], in the case of isopropenylbicycloheptene proved to be incorrect, since in this case, when isopropenylbicycloheptene isomerized, 1-methyltetrahydroindene should have been formed (with a methyl group in the five-membered ring), but actually 5-methyltetrahydroindene was formed (with the methyl group in the six-membered ring).

The formation in the condensation of cyclopentadiene with isoprene and in the isomerization of 2-isopropenylbicycloheptene-5 of the same 5-methyltetrahydroindene favors the conclusion that both the condensation and the isomerization proceed through one common intermediate step.

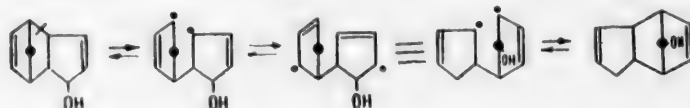
We are inclined to assume that the condensation of cyclopentadiene with butadiene or isoprene proceeds in the same way as has been proposed for the dimerization of isoprene [16], through the intermediate formation of biradicals. The latter either may be stabilized and then one of the codimers formed, or may be first isomerized by way of an allyl shift of the double bonds and only then stabilized and the other codimer subsequently formed.



Thus, when vinyl- or isopropenylbicycloheptene is isomerized, the rupture of the C-C bond which is one carbon away from the two double bonds occurs (according to O. Schmidt's rule) and the biradical A that is formed undergoes isomerization to the biradical B and then is stabilized.

This new type of thermal isomerization is apparently a specific property of vinylbicycloheptene and its homologs, since neither 2-ethylbicycloheptene-5 nor 2-vinylbicycloheptane,* nor 2-ethylbicycloheptane undergo a similar sort of conversion under these conditions.

It is very probable that the isomerization of 1-hydroxydicyclopentadiene to 8-hydroxydicyclopentadiene takes place by a similar scheme, which as indicated in the literature [17] also proceeds by way of dissociation to cyclopentadiene and hydroxycyclopentadiene. If the mechanism proposed by us is correct, the isomerization of 1-hydroxycyclopentadiene can be represented in the following way:



The fact that when cyclopentadiene is condensed with butadiene an increase in the reaction temperature results in an increase in yield of tetrahydroindene and a corresponding decrease in yield of vinylbicycloheptene [13] is associated with capacity of the latter to isomerize to tetrahydroindene. Comparison of the yields of tetrahydroindene obtained when vinylbicycloheptene is isomerized with the relative yields of these hydrocarbons in the synthesis, however, shows that the degree of conversion of vinylbicycloheptene to tetrahydroindene is less than the increase in yield of the latter when the temperature of the reaction is increased. From this it follows that the increase in the yield of tetrahydroindene occurs not only at the expense of isomerization of vinylbicycloheptene but also that a certain portion of the tetrahydroindene is a primary product of reaction of cyclopentadiene with butadiene.

EXPERIMENTAL

Isomerization of 2-vinylbicyclo[2.2.1]heptene-5 to tetrahydroindene. a) Thirty-three grams of vinylbicycloheptene was passed at 300° with a velocity of 4.5 g/hour through a quartz tube (length 80 cm and diameter 14 mm) filled with broken quartz. Thirty and four tenths grams of condensate was obtained, from which we obtained by fractional distillation 6.7 g of butadiene (identified in the form of the adduct with maleic anhydride, m.p. 101-102° from petroleum ether [18]), 6.3 g of cyclopentadiene (b.p. 40-41°, adduct with maleic anhydride m.p. 160.5-162.5° [19]), 15.2 g of tetrahydroindene (b.p. 74.1-74.3° at 44 mm, n_D^{20} 1.4982, d_4^{20} 0.9266), and traces (0.3 g) of the starting vinylbicycloheptene.

b) Thirteen and seven tenths grams of vinylbicycloheptene (n_D^{20} 1.4807) was heated in a sealed ampoule at 150° for 12 hours. From the product which was removed (13.3 g, n_D^{20} 1.4840) we obtained on distillation 12.0 g of a mixture of vinylbicycloheptene (93%) and tetrahydroindene (7%) with b.p. 139-145° and n_D^{20} 1.4818. The residue after distillation (1.0 g) had n_D^{20} 1.5088 and was a higher molecular weight compound.

c) By heating 11.0 g of vinylbicycloheptene in a sealed ampoule at 170° for 5 hours we obtained 9.0 g of a mixture of 57% vinylbicycloheptene and 43% of tetrahydroindene (b.p. 144-160°, n_D^{20} 1.4880).

d) Six and six tenths grams of vinylbicycloheptene was refluxed in a flask in an atmosphere of nitrogen for 88 hours. By distillation of the product obtained (5.7 g) we isolated 4.5 g of a mixture of vinylbicycloheptene and tetrahydroindene with b.p. 140-156°, n_D^{20} 1.4925, d_4^{20} 0.9170. The residue from the fractional distillation (1.2 g) was a higher molecular weight compound. Judged by the index of refraction and the specific gravity, the mixture of hydrocarbons obtained consisted of 31% of vinylbicycloheptene and 69% of tetrahydroindene. According to Raman spectral data the mixture consisted of 25% vinylbicycloheptene and 75% of tetrahydroindene.

When an equimolecular mixture of cyclopentadiene and butadiene was passed through a quartz tube at 168 and 300° at a velocity of 3 g/hour, a mixture of the starting hydrocarbons was obtained.

Isomerization of 2-isopropenylbicyclo[2.2.1]heptene-5. Thirty-five and eight tenths grams of isopropenylbicycloheptene (n_D^{20} 1.4862) was passed through a quartz tube at 300° with a velocity of 6 g/hour. Thirty-three and nine tenths grams of condensate was obtained, from which we separated by distillation on a column 8.8 g of a mixture of cyclopentadiene and isoprene (b.p. 34-40°, n_D^{20} 1.4380), 0.4 g of the starting isopropenylbicycloheptene (b.p. 64.2-69.7°, n_D^{20} 1.4849), and 23.7 g of 5-methyltetrahydroindene.

* 2-Vinylbicyclo[2.2.1]heptane was prepared by us by pyrolysis of the acetate of 2-(2-bicyclo[2.2.1]heptyl)ethanol-1 at 430°; formation of an isomerization product was not observed under these conditions.

B.p. 75.5° (21 mm), 181° (760 mm), n_D^{20} 1.4932, d_4^{20} 0.9097, M_R 42.90; calc. 43.04.

Found %: C 89.51, 89.42; H 10.62, 10.41. $C_{10}H_{14}$. Calculated %: C 89.48; H 10.51.

On dehydrogenation of the methyltetrahydroindene thus obtained over platinized carbon at 310-315° with a volume velocity of 0.2 we obtained 5-methylindane.

B.p. 93.0° (21 mm), n_D^{20} 1.5330, d_4^{20} 0.9465. Literature data [18]: b.p. 201.1° (740.5 mm), n_D^{25} 1.5311, d_4^{25} 0.9442.

When 20.6 g of an equimolar mixture of cyclopentadiene and isoprene was passed through a quartz tube at 300° at the rate of 4 g/hour, we obtained 16.6 g of the starting mixture of cyclopentadiene and isoprene with b.p. 35-38°, n_D^{20} 1.4330.

Study of the thermal stability of 5-ethylbicyclo[2.2.1]heptene-2 and 2-ethylbicyclo[2.2.1]heptane. a) Seven and nine tenths grams of ethylbicycloheptene* (b.p. 140-142°, n_D^{20} 1.4648) was passed through a quartz tube at 300° with a velocity of 4.3 g/hour. From the condensate (6.6 g) we obtained by fractional distillation 0.5 g of a very volatile compound, which apparently was butene-1, 0.6 g of cyclopentadiene (n_D^{20} 1.4420), and 4.8 g of the starting ethylbicycloheptene (b.p. 139-142°, n_D^{20} 1.4664). The somewhat high index of refraction of the regenerated ethylbicycloheptene is explained by the presence in it of a trace of dicyclopentadiene. Thus, under these conditions only a slight decomposition of ethylbicycloheptene to cyclopentadiene and butene occurs (~15%), and the main portion of it is unchanged (~85%).

b) Five and nine tenths grams of 2-ethylbicyclo[2.2.1]heptane (n_D^{20} 1.4568) was passed through a tube at 300° with a velocity of 5 g/hour. The condensate obtained (5.05 g) had b.p. of 151.6° (745 mm), n_D^{20} 1.4567.

SUMMARY

1. The thermal conversion of 2-vinyl- and 2-isopropenylbicyclo[2.2.1]heptene-5 has been studied, and it has been shown that at 150-300° they are converted to 4,9,7,8-tetrahydroindene and 5-methyl-4,9,7,8-tetrahydroindene, respectively.

2. The isomerization studied is apparently a specific property of 2-vinylbicyclo[2.2.1]heptene-5 and its homologs, since neither 5-ethylbicyclo[2.2.1]heptene-2, 2-vinylbicyclo[2.2.1]heptane nor 2-ethylbicyclo[2.2.1]heptane undergo such conversions under these conditions.

3. A possible isomerization mechanism has been suggested.

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*5-Ethylbicyclo[2.2.1]heptene-2 was prepared by A. F. Platé and I. L. Safonova by condensation of cyclopentadiene with butene-1 [20].

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INVESTIGATION IN THE FURAN SERIES.

XI. 2,5-BIS(CHLOROMETHYL)FURAN IN THE SYNTHESIS OF SYMMETRICAL 2,5-DIALKYLFURANS

K. Yu. Novitskii, V. P. Volkov, L. P. Shalderova, and Yu. K. Yur'ev

Moscow State University

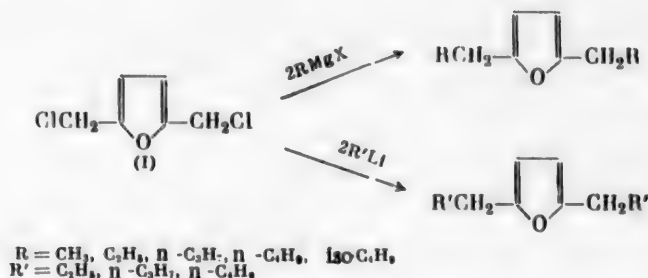
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 1, pp. 136-139,

January, 1961

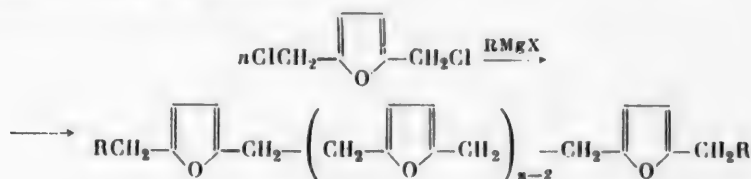
Original article submitted February 22, 1960

In our previous communications [1, 2] we described the preparation of symmetrical diamines [1], ethers and thioethers [2] of the furan series from 2,5-bis(chloromethyl)furan. In the present work we used this compound for the synthesis of symmetrical 2,5-dialkylfurans, which, with the exception of 2,5-dimethylfuran [3], the most available and therefore studied in the most detail, were unknown until recently. Thus, 2,5-diethyl- and 2,5-dipropylfuran were prepared only in 1953 by the acylation of α -ethyl- and α -propylfuran, respectively, with subsequent reduction of the 5-alkyl-2-acylfurans which were formed [4]. 2,5-Di(tert-butyl)furan was prepared in low yield in 1957 [5] by the alkylation of furan with isobutylene in the presence of boron fluoride etherate. 2,5-Di(tert-amyl)furan has been described as a by-product formed in the alkylation of furan with isoamylene [6].

To prepare the symmetrical 2,5-dialkylfurans we reacted 2,5-bis(chloromethyl)furan (I) with organomagnesium compounds and established that the 2,5-dialkylfurans are obtained in 33-56% yield and that the yield depends essentially on both the length of the carbon chain and the nature of the halogen of the alkylmagnesium halide. The highest yield of dialkylfurans was obtained in working with alkylmagnesium chlorides (46% with propylmagnesium chloride and 38% with butylmagnesium chloride); in the case of the alkylmagnesium bromides the yield fell to 37% with propylmagnesium bromide and 29% with butylmagnesium bromide, and with methylmagnesium iodide it was only about 5%.



With the Grignard reagents from *n*-octyl bromide, bromobenzene, benzyl chloride, cyclopentyl- and cyclohexyl chlorides there was no success; the reaction products were undistillable and uncrystallizable tarry materials. In the case of phenylmagnesium bromide and benzylmagnesium chloride we were also able to isolate biphenyl (5%) and symmetrical diphenylethane (18%), respectively. According to the data in the literature, when methylmagnesium iodide acts on furfuryl chloride, symmetrical difurylthane is obtained in 50% yield, instead of the expected ethylfuran [7]. In the reaction described by us, the competing process was a polycondensation of the same type, which should lead to polymers of the following structure:



When 2,5-bis(chloromethyl)furan reacted with lithium alkyls, the yields of the corresponding dialkylfurans were 19-25%. When 2,5-bis(chloromethyl)furan was reduced in the presence of palladium on barium sulfate, we obtained 2,5-dimethylfuran in 55% yield.

EXPERIMENTAL

Reaction of 2,5-Bis(chloromethyl)furan (I) with Alkylmagnesium Halides

In a 500-ml three-necked flask with a reflux condenser, stirrer, and dropping funnel was placed a solution of 0.12 mole of alkylmagnesium halide in 200 ml of absolute ether, and to it was added dropwise, during 1.5-2 hours at 25°, a solution of 0.05 mole of compound (I) in 25 ml of ether. The mixture was boiled for 4-5 hours, cooled, and decomposed with 10% ammonium chloride solution. The ether layer was separated and the aqueous layer was extracted three times with ether. The ether extracts were combined, washed with water, and dried with magnesium sulfate. After the ether had been distilled off, the residue was distilled in vacuum over sodium.

2,5-Diethylfuran. a) From 8.25 g of compound (I), 2.65 g of magnesium, and 11.4 g of methyl bromide we obtained 3.5 g (56%).

B.p. 70-71° (75 mm), n_D^{20} 1.4510, d_4^{20} 0.8864, MR_D 37.71. $C_8H_{12}OF_2$. Calculated 37.65.

Found %: C 77.20, 77.27; H 9.73, 9.81. $C_8H_{12}O$. Calculated %: C 77.39; H 9.74.

b) From 8.25 g of compound (I), 2.65 g of magnesium, and 17.0 g of methyl iodide we obtained 0.32 g (5%).

B.p. 64-65° (55 mm), n_D^{20} 1.4514, d_4^{20} 0.8860, MR_D 37.77.

Literature data: b.p. 138° (758 mm), n_D^{15} 1.4548.

2,5-Dipropylfuran. From 8.25 g of compound (I), 2.65 g of magnesium, and 13.1 g of ethyl bromide we obtained 3.35 g (44%).

B.p. 66-67° (13 mm), n_D^{20} 1.4533, d_4^{20} 0.8802, MR_D 46.77. $C_{10}H_{16}OF_2$. Calculated 46.89.

Found %: C 78.69, 78.87; H 10.75, 10.82. $C_{10}H_{16}O$. Calculated %: C 78.91; H 10.60.

Literature data: b.p. 173° (756 mm), n_D^{16} 1.4543.

2,5-Dibutylfuran. a) From 8.25 g of compound (I), 2.65 g of magnesium, and 9.3 g of propyl chloride we obtained 4.15 g (46%).

B.p. 74-75° (5 mm), n_D^{20} 1.4545, d_4^{20} 0.8687, MR_D 56.25. $C_{12}H_{20}OF_2$. Calculated 56.12.

Found %: C 79.70, 79.86; H 11.28, 11.32. $C_{12}H_{20}O$. Calculated %: C 79.93; H 11.18.

b) From 8.25 g of compound (I), 2.65 g of magnesium, and 14.7 g of propyl bromide we obtained 3.35 g (37%).

B.p. 76-77° (6 mm), n_D^{20} 1.4547, d_4^{20} 0.8686, MR_D 56.27.

2,5-Diamylfuran. a) From 8.25 g of compound (I), 2.65 g of magnesium, and 11 g of butyl chloride we obtained 3.95 g (38%).

B.p. 99-100° (5 mm), n_D^{20} 1.4570, d_4^{20} 0.8702, MR_D 65.20. $C_{14}H_{24}OF_2$. Calculated 65.36.

Found %: C 80.70, 80.84; H 11.20, 11.38. $C_{14}H_{24}O$. Calculated %: C 80.72; H 11.61.

b) From 8.25 g of compound (I), 2.65 g of magnesium, and 16.5 g of butyl bromide we obtained 3.0 g (29%).

B.p. 96-97° (4 mm), n_D^{20} 1.4572, d_4^{20} 0.8700, MR_D 65.24.

2,5-Diisobutylfuran. From 8.25 g of compound (I), 2.65 g of magnesium, and 16.5 g of isobutyl bromide we obtained 3.45 g (33%).

B.p. 74-75° (2 mm), n_D^{20} 1.4565, d_4^{20} 0.8714. MR_D 65.05. $C_{14}H_{24}OF_2$. Calculated 65.36.

Found %: C 80.69, 80.93; H 11.66, 11.70. $C_{14}H_{24}O$. Calculated %: C 80.72; H 11.61.

Reaction of 2,5-Bis(chloromethyl)furan (I) with Lithium Alkyls

As described above, to a solution of 0.10-0.12 mole of lithium alkyl in 150 ml of absolute ether [8] cooled with ice water was added dropwise during 1 hour a solution of 0.05 mole of compound (I) in 25 ml of ether. After the cooling water had been removed, the mixture was stirred for 2 hours, boiled for 30 minutes, cooled, and decomposed with 2 N acetic acid. The ether extracts were washed with sodium carbonate and with water, and dried with magnesium sulfate. After the ether had been distilled off, the residue was distilled in vacuum over sodium.

2,5-Dipropylfuran. From 8.25 g of compound (I), 3.5 g of lithium, and 27.3 g of ethyl bromide we obtained 1.9 g (25%).

B.p. 59-60° (8 mm), n_D^{20} 1.4534, d_4^{20} 0.8808, MR_D 46.76.

2,5-Dibutylfuran. From 8.25 g of compound (I), 3.5 g of lithium, and 30.7 g of propyl bromide we obtained 1.9 g (21%).

B.p. 70-71° (4 mm), n_D^{20} 1.4543, d_4^{20} 0.8689, MR_D 56.22.

2,5-Diamylfuran. From 8.25 g of compound (I), 3.5 g of lithium, and 34.3 g of butyl bromide we obtained 2.1 g (19%).

B.p. 91-92° (3 mm), n_D^{20} 1.4574, d_4^{20} 0.8700, MR_D 65.26.

Reduction of 2,5-Bis(chloromethyl)furan (I)

Two and five tenths grams of compound (I) and 1.85 g of potassium hydroxide were dissolved in 30 ml of 80% acetone and hydrogenated in the cold with shaking in the presence of palladium on barium sulfate. In 3 hours 500 ml (STP) of hydrogen (75%) was absorbed. After the catalyst had been removed, the filtrate was treated with excess saturated sodium bisulfite solution, filtered, and the filtrate extracted with ether; the extracts were dried with magnesium sulfate, the ether was distilled off, and the residue was distilled over sodium. We obtained 0.8 g (55%) of 2,5-dimethylfuran.

B.p. 94-95° (742 mm), n_D^{20} 1.4425, d_4^{20} 0.8955, MR_D 28.43. C_6H_8O . Calculated 28.42.

Literature data: B.p. 94.5-95.5° (755 mm), n_D^{20} 1.4419, d_4^{20} 0.8950, MR_D 28.39 [9].

SUMMARY

The reaction of 2,5-bis(chloromethyl)furan with alkylmagnesium halides can serve as a method of synthesis of simple symmetrical dialkylfurans up to 2,5-diamylfuran, inclusive. The use in this reaction of alkylmagnesium chlorides ensures obtaining good yields.

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USE OF THE HAMMETT EQUATION FOR PHOSPHORUS DITHIO ACIDS

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The well-known linear relationship of Hammett [1]:

$$\lg \frac{k}{k^0} = \rho \sigma$$

is properly used for reaction rate constants and equilibrium constants of aromatic compounds of the type:

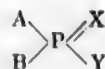


Here k and k^0 are rate or equilibrium constants characterizing the substituted (substituent A) and unsubstituted ($A = H$) aromatic derivative; σ is a constant characteristic of the substituent A and its position in relation to the reacting group Y and independent of the type of reaction; ρ is the reaction constant.

It has recently been shown in our laboratory [2] that the equation

$$\lg \frac{k}{k^0} = \rho \Sigma \sigma$$

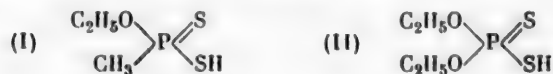
is well maintained for organophosphorus compounds of the general type:



The role of the carrying system is played here by the group $P = X$ (X is oxygen or sulfur) instead of by the benzene rings; A and B are groups of atoms joined to phosphorus and characterized each by its own value of σ . For the unsubstituted standard, the corresponding (sometimes hypothetical) hydrogen compound is taken ($A = B = H$). Naturally the constants σ for the organophosphorus compounds of the indicated type with its specific carrying system differ from the Hammett constants σ .

The linear relationship shown was verified for the ionization constants of oxygen acids of phosphorus ($X = O$; $Y = OH$) [2, 3] and also of the monothio acids of phosphorus ($X = S$; $Y = OH$) [4] in water, 7, 50, and 80% alcohol, and for the protolysis constants of the phosphorus acids with the base of hexamethoxy red in benzene and chlorobenzene [5]. In all cases a good linear relationship was observed with the coefficients of correlation not less than 0.95.

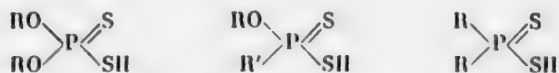
Several years ago Godovikov [6] synthesized a dithio acid of structures (I):



Its ionization constant in water at 20° (pK 1.68) proved to be practically the same as the ionization constants of diethyldithiophosphoric acid (II) (pK 1.62) [7]. If we compare with this the fact of the great difference in $\Sigma \sigma$ for these compounds (in the first case $\Sigma \sigma$ is -1.179, and in the second it is -0.428), then we might come to the

conclusion that Hammett's rule is not maintained for the dithio acids of phosphorus. We therefore undertook a special investigation of this question.

We synthesized 16 dithio acids of phosphorus of three types:



Some of these acids have been described in the literature, but some of them were prepared for the first time. For all the acids we measured the ordinary (apparent) ionization constants in 7 and 80% aqueous alcohol (Table 1). It can be seen from the data in Table 1 that an astonishingly constant pK is observed for the dithio acids of phosphorus independent of the nature of the substituents A and B. On the coordinates pK and $\Sigma\sigma$ (Fig. 1) straight lines are obtained almost parallel with the abscissa axis. For 7% aqueous alcohol ρ is 0.0007, $\log k_0 = 1.74$; for 80% aqueous alcohol the corresponding values are 0.022 and 2.64.

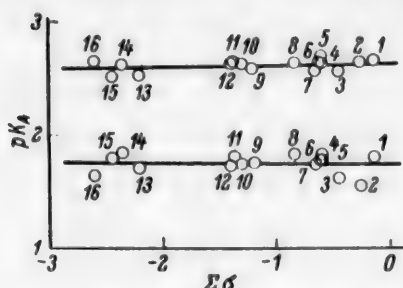
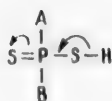


Fig. 1. Relationship of ionization constant of phosphorus dithio acid ABPSSH to $\Sigma\sigma$ in 7% (lower straight line) and 80% (upper straight line) alcohol at 20°. For numbering of points see Table 1.

We may speak of the effect of the substituents on the condition of solvation of the ions and the molecules, etc. If the different effects summarized lead to mutual compensation, then the observed independence of the ionization constants from the nature of the substituents does not indicate the absence of these effects, and Hammett's rule is applicable to the systems under consideration in the exceptional case where ρ is equal or close to zero.

The choice between these two hypotheses may be made on the basis of an investigation of the relationship of the constants of other reactions of the phosphorus dithio acids to the nature of the substituents A and B. If the

Hammett rule is not applicable to the phosphorus dithio acids and the system $\text{>P} \begin{array}{l} \diagup \text{S} \\ \diagdown \text{S-} \end{array}$ is en-



tirely incapable of transmitting the effect of the substituents A and B to the S-H bond, then the constants of the other reaction also should not be dependent on the nature of A and B. If, however, the Hammett rule is applicable to the system under consideration, and internal compensation of the effects (for example, those assumed above) occurs only in the case of the ionization constants, then it is completely improbable that full internal compensation of effects

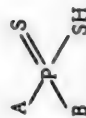
and independence of $\log k$ from $\Sigma\sigma$ would again take place for other reactions. In other words, when the type of reaction was changed, we could calculate on the basis of the usual linear Hammett relationship with the tangent of the angle of slope differing from zero.

We determined the pseudomonomolecular rate constants of benzylation of the sodium salts of the phosphorus dithio acids with benzyl chloride in 95.5% alcohol at 25° (Table 2). It can be seen that the reproducibility of the results in replicate experiments was good, and if we do not count compounds 7 and 9, the rate constants increase regularly with a decrease in $\Sigma\sigma$. In Fig. 2 the relationship of $\log k$ to $\Sigma\sigma$ is shown graphically. It corresponds to a straight line with $\tan \alpha = \rho = -0.236$ and $\log k^0 = -3.87$. The coefficient of correlation $r = 0.964$.

Thus, the Hammett equation is applicable to the rate constants of benzylation of the salts of the phosphorus dithio acids with the previously reported constants σ [2, 3] of the substituents. If we compare with these data the

TABLE 1

Phosphorus Dithio A cids



Com- pound No.	A	B	Boiling point (pressure in mm)	n_D^{20}	d_4^{20}	Neutralization equivalent*		pK_{20}	
						found	calculated	7% alcohol	80% alcohol
1	$\text{C}_6\text{H}_5\text{O}$	$\text{C}_6\text{H}_5\text{O}$	M.p. 60–61°	—	—	281.9, 282.2	282.2	1.81	2.66
2	CH_3O	CH_3O	56–57° (4)	1.5340	1.2869	157.6, 158.4	158.1	1.55	2.64
3	$\text{C}_2\text{H}_5\text{O}$	$\text{C}_2\text{H}_5\text{O}$	77–78° (4)	1.5073	1.1651	185.3, 186.1	186.2	1.62	2.56****
4	$\text{Iso-C}_3\text{H}_7\text{O}$	$\text{Iso-C}_3\text{H}_7\text{O}$	71–72° (3)	1.4918	1.0911	214.3, 213.8	214.3	1.82	2.65
5	$\text{P-ClC}_6\text{H}_4$	$\text{P-ClC}_6\text{H}_4$	M.p. 82–83°	—	—	318.7, 318.2	319.2	1.79	2.69
6	$\text{Iso-C}_4\text{H}_9\text{O}$	$\text{Iso-C}_4\text{H}_9\text{O}$	77.5–78 (1.5)	1.4921	1.0620	242.0, 242.3	242.3	1.79****	2.65****
7	$\text{n-C}_3\text{H}_7\text{O}$	$\text{n-C}_3\text{H}_7\text{O}$	85–86° (3)	1.4987	1.1040	213.5, 213.3	214.3	1.75	2.57
8	$\text{n-C}_4\text{H}_9\text{O}$	$\text{n-C}_4\text{H}_9\text{O}$	99–99.5 (2)	1.4971	1.0722	242.3, 242.0	242.3	1.83	2.64
9	C_6H_5	C_6H_5	M.p. 56°	—	—	250.2, 250.4	250.3	1.75	2.60
10	CH_3	$\text{n-C}_3\text{H}_7\text{O}$	M.p. 62–63°**	—	—	190.9, *** 191.2	192.2	1.74	2.63
11	$\text{P-CH}_2\text{C}_6\text{H}_4$	$\text{P-CH}_2\text{C}_6\text{H}_4$	M.p. 80–81°	—	—	278.9, 278.5	278.4	1.81	2.65
12	CH_3	$\text{n-C}_4\text{H}_9\text{O}$	60.5–62 (0.5)	1.5298	—	184.3, 184.6	184.2	1.73	2.63
13	C_2H_5	C_2H_5	M.p. 122.5– 124°**	—	—	179.1, *** 178.2	176.2	1.71	2.53
14	$\text{n-C}_3\text{H}_7$	$\text{n-C}_3\text{H}_7$	91–91.5 (2)	1.5632	1.0891	181.4, 181.9	182.3	1.84	2.63
15	$\text{n-C}_4\text{H}_9$	$\text{n-C}_4\text{H}_9$	99–99.5 (2)	1.5481	1.0314	210.7, 209.1	210.4	1.79	2.52
16	$\text{Iso-C}_3\text{H}_7$	$\text{Iso-C}_3\text{H}_7$	M.p. 153– 154.5°**	—	—	206.6, *** 204.2	204.3	1.74	2.66

* With respect to thymolphthalein.

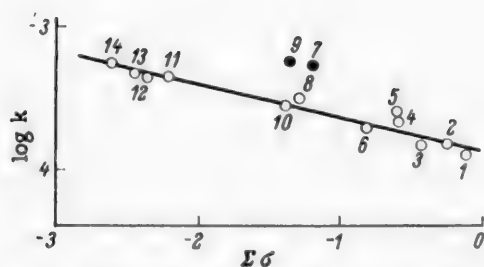
** Sodium salt.

*** The iodometric equivalent of the salt was determined.

**** Values are given which are defined more accurately in comparison with [7].

Rate Constants of Benzylation, $k[\text{sec}^{-1}]$, of Salts ABPSSNa with Benzyl Chloride in 95.5% Alcohol at 25°

Compound No.	A	B	k (sec ⁻¹) · 10 ⁴		Σ
			found	average	
1	C ₆ H ₅ O	C ₆ H ₅ O {	1.29 1.16	1.23	-0.128
2	CH ₃ O	CH ₃ O {	1.37 1.48	1.43	-0.248
3	C ₂ H ₅ O	C ₂ H ₅ O {	1.40 1.47	1.44	-0.428
4	p-ClC ₆ H ₄	p-ClC ₆ H ₄ {	2.43 2.71 2.11	2.42	-0.584
5	iso-C ₄ H ₉ O	iso-C ₄ H ₉ O {	2.31 2.67	2.49	-0.600
6	n-C ₄ H ₉ O	n-C ₄ H ₉ O {	1.89 1.95	1.92	-0.822
7	C ₆ H ₅	C ₆ H ₅ {	5.26 5.21 5.27	5.25	-1.184
8	CH ₃	n-C ₃ H ₇ O {	3.07 3.45	3.11	-1.280
9	p-CH ₃ C ₆ H ₄	p-CH ₃ C ₆ H ₄ {	5.73 5.56	5.65	-1.348
10	CH ₃	n-C ₄ H ₉ O {	2.92 2.60	2.76	-1.376
11	C ₂ H ₅	C ₂ H ₅ {	4.26 4.49	4.37	-2.202
12	n-C ₃ H ₇	n-C ₃ H ₇ {	4.13 4.55	4.34	-2.354
13	n-C ₄ H ₉	n-C ₄ H ₉ {	4.79 4.66	4.73	-2.438
14	iso-C ₃ H ₇	iso-C ₃ H ₇ {	5.34 5.77	5.56	-2.600



results of measurement of the constants of protolysis of the phosphorus dithio acids with the base of hexamethoxy red in benzene and chlorobenzene, obtained by two of us and Ioffe [5], to which the Hammett equation also is normally applicable, then we may arrive at the conclusion that the Hammett equation is applicable to the reactions of the phosphorus dithio acids and that the constancy of the ionization constants of the phosphorus dithio acids in water and their independence of the nature of the substituents A and B are the results of internal compensation of effects (possibly by the mechanism considered above).

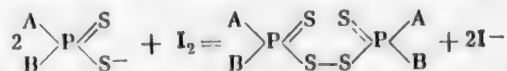
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presence of one aryl group on the phosphorus. When there are two such groups, the value of σ changes because of steric reasons.* Apparently the magnitude of this change depends on the type of reaction. These deviations can be compared with the known deviations from the linear Hammett relationship for ortho-substituted aromatic compounds, where the value of σ also is not constant [8].

EXPERIMENTAL

Determination of ionization constants of the phosphorus dithio acids was carried out in 7 and 80% aqueous alcohol in circuits with liquid contacts, using an LP-5 potentiometer and a glass electrode; temperature 20°. The concentrations used were 5×10^{-3} M. The apparatus was balanced with respect to a diphthalate buffer with pH 4.00. The value of pK was calculated by Kumler's method [9] without correcting for the activity; thus, the apparent ionization constants were determined.

Reaction rate constants of benzylation of the sodium salts of the phosphorus dithio acids were determined** in 95.5% alcohol at $25 \pm 0.1^\circ$. The concentrations of the salts were 0.02-0.05 M; benzyl chloride was used in ten times excess. The course of the reaction was followed by taking aliquot samples; the unreacted salt was converted by acidification to the dithio acid, which was oxidized with iodine to the disulfide.



The excess iodine was titrated with sodium thiosulfate. The analytical method was first checked on artificial mixtures and compared with the data from acidimetric determinations. The pseudomonomolecular rate constants were calculated by the usual first order equation $\log \frac{a}{a-x} = kt$, using the method of least squares.

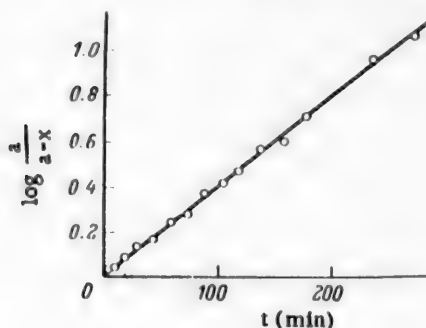


Fig. 3. Relationship of $\log \frac{a}{a-x}$ to t for the benzylation of the sodium salt of dimethyldithiophosphoric acid with benzyl chloride at 25° in 95.5% alcohol.

In Figure 3 the results of a typical experiment are shown on the coordinates $\log \frac{a}{a-x}$ and t . The parameters of the Hammett equation given above were calculated by the method of least squares, but the values corresponding to points 7 and 9 were not included in the calculations.

SUMMARY

1. The ordinary (apparent) ionization constants of the phosphorus dithio acids were measured at 20° in 7 and 80% alcohol, and the rate constants for the benzylation of the sodium salts of these acids in 95.5% alcohol with benzyl chloride at 25° were determined.

2. It was shown that the Hammett equation, $\log \frac{k}{k^0} = \rho \Sigma \sigma$ is applicable to the ionization constants and the reaction constants for benzylation with the constants σ obtained previously.

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*A similar effect also should be expected for the p-chlorophenyl group. As a result of the small absolute value of σ (-0.292), however, the changes caused in it by steric factors also are slight.

**With the assistance of Student S. Leimane of the Riga Polytechnic Institute.

IODONIUM DERIVATIVES OF β -DIKETONES

IV. REACTION OF 5-PHENYLCYCLOHEXANEDIONE-1,3 WITH PHENYL IODOSOACETATE

O. Ya. Neiland and G. Ya. Vanag

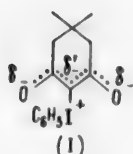
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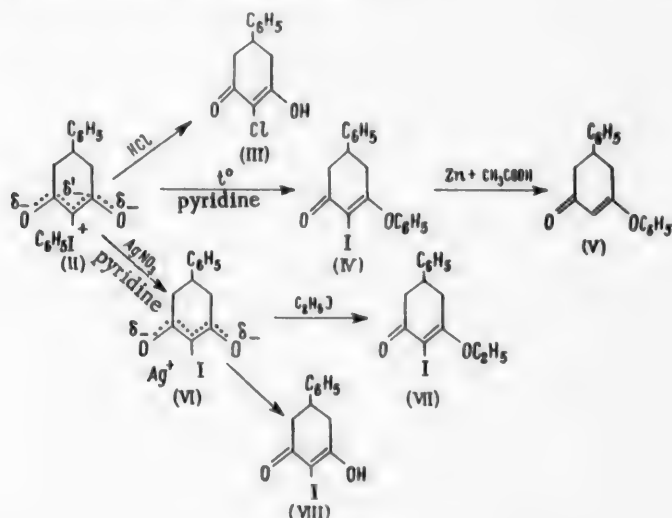
In the reaction of dimedone (5,5-dimethylcyclohexanedione-1,3) with phenyl iodosoacetate, a compound of the type of an internal iodonium salt is formed, which has been called an iodone (I) [1, 2]. For a study of the adaptability of this reaction to other β -dicarbonyl compounds, we selected 5-phenylcyclohexanedione-1,3, which is very similar to dimedone in its properties. We found that phenyl iodosoacetate reacts very easily with 5-phenylcyclohexanedione-1,3 with the formation of the phenyliodone (II).



The phenyliodone is a colorless compound, which crystallizes as very long, thin needles that form a feltlike mass. In contrast to the iodone, we were not able to prepare the hydrate of the phenyliodone or its adducts with acids in the pure form. When we attempted to prepare the hydrogen chloride adduct of the phenyliodone, a decomposition product of the latter was formed—2-chloro-5-phenylcyclohexanedione-1,3 (III). Since when 5-phenylcyclohexanedione-1,3 is chlorinated the 2,2-dichloro derivative always is formed [3], the decomposition of the phenyliodone with the aid of hydrochloric acid may prove to be a convenient method of preparing the monochloro derivative, which has not been described previously in the literature. We also

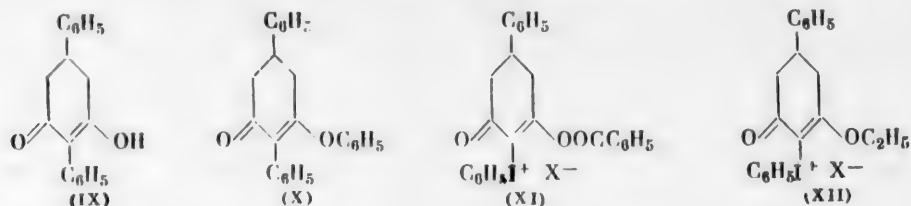
succeeded in bringing about the rupture of the bond between the iodine and the phenyl group. When the phenyliodone was boiled in pyridine, 1-iodo-2-phenoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -one-6 (IV) was formed. We must assume that this cleavage represents an intramolecular heterolytic process and the phenyl cation is not formed as an independent particle. In the opposite case we would have to expect the formation of N-phenylpyridinium salts, which is not observed.

1-Iodo-2-phenoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -one-6 readily splits out iodine under the influence of zinc dust in glacial acetic acid. The 2-phenoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -one-6 (V) thus obtained is hydrolyzed by hydrochloric acid with the formation of phenol and 5-phenylcyclohexanedione-1,3.



In the presence of silver nitrate and pyridine the phenyliodone was smoothly cleaved and the silver salt of 2-iodo-5-phenylcyclohexanedione-1,3 (VI) was formed, and it was converted to 1-iodo-2-ethoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -one-6 (VII) and 2-iodo-5-phenylcyclohexanedione-1,3 (VIII). It must be assumed that in this cleavage reaction the main role is played by the low solubility of the silver salt of 2-iodo-5-phenylcyclohexanedione-1,3 and the ability of pyridine to solvate the carbon atom [4], thus facilitating the rupture of the carbon-iodine bond.

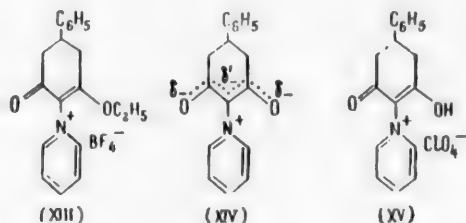
As in the work with dimedone [5], experiments on the direct phenylation of 5-phenylcyclohexanedione-1,3 were set up. The phenylation did not go smoothly, and we were able to isolate in the pure form from the tarry reaction products only 2,5-diphenylcyclohexanedione-1,3 (IX) and 2-phenoxy-1,4-diphenylcyclohexan- $\Delta^{1,2}$ -one-6 (X) in small yields. 2,5-Diphenylcyclohexanedione-1,3 (IX) is not known in the literature, but the structure of compound (X) was demonstrated by cleavage to phenol and compound (IX).



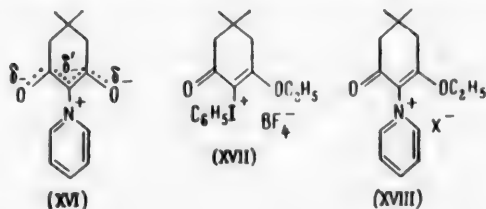
The phenyliodone, like the iodone [2], is easily acylated and alkylated. The products obtained were low in stability. When acylation was carried out with acetyl chloride, only 2-chloro-5-phenylcyclohexanedione-1,3 (III) was obtained.

When the phenyliodone reacted with benzoyl chloride, the benzoate (XI, $X = Cl$) was formed, and it was very easily decomposed; in aqueous methanol solution the chlorine anion could be replaced by bromine. The bromide (XI, $X = Br$) was more stable. By alkylation of the phenyliodone with triethyloxonium borofluoride we were able to obtain the borofluoride (XII, $X = BF_4$), which was a colorless amorphous powder, and which we were unable to obtain in the crystalline form. In aqueous methanol solution it was possible to obtain the corresponding bromide (XII, $X = Br$) by an exchange reaction with potassium bromide; the bromide was a crystalline compound which gradually decomposed on standing.

We investigated the decomposition of the borofluoride (XII, $X = BF_4$) in the presence of pyridine, since it is well known that diaryliodonium borofluorides under such conditions are cleaved with the formation of N-arylpyridinium borofluorides [6].



It turned out that decomposition proceeded easily and a compound was formed which was assigned the structure of the borofluoride (XIII). When the latter was hydrolyzed, the N-(5-phenylcyclohexanedione-1,3-yl-2) pyridinium enolate-betaine (XIV) was obtained. It is interesting to note that the same enolate-betaine is obtained when 2-bromo-5-phenylcyclohexanedione-1,3 reacts with pyridine; 2-bromodimedone with pyridine forms only tarry products. A similar enolate-betaine of dimedone (XVI) could be obtained, as already reported [7], by the cleavage of the borofluoride (XVII) in the presence of pyridine and hydrolysis of the borofluoride (XVIII, $X = BF_4$) which was formed.



The borofluorides (XIII and XVIII, $X = \text{BF}_4$) and the perchlorate (XVIII, $X = \text{ClO}_4$) have some peculiarities. Thus, very high results are always obtained from the microdetermination of nitrogen. In order to characterize these compounds, in addition to the infrared spectra we determined the borofluoride or perchlorate anion content. The properties of the corresponding dimedone derivatives were more carefully studied. The borofluoride (XVIII, $X = \text{BF}_4$) for unknown reasons can exist in two modifications with different melting points (120 and 140°), but with the same properties and infrared spectra. The conditions for the transition of one modification to the other could not be ascertained. A mixture of the modifications did not give a depression in melting point, but fused partially at 120° and completely melted at 140° .

The pyridinium salts (XIII) and (XVIII) instantly gave a dark red color with alkalis, which was maintained for hours in dichloroethane solutions, but disappeared in a few seconds in aqueous solutions. It is possible that the color is dependent on the opening of the pyridine ring with the formation of derivatives of glutaric aldehyde, in a manner similar to some other N-derivatives of pyridine containing substituents on the nitrogen atom with strongly expressed electron acceptor properties [8].

The enolate-betaines (XIV) and (XVI) were dark yellow crystalline compounds which readily formed dihydrates and colorless adducts with acids (perchlorate XV). All the properties agreed completely with the already known N-(dibenzoylmethyl)pyridinium enolate-betaine [9].

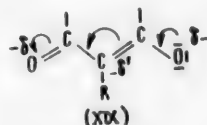
N-Dimedonylpyridinium enolate-betaine (XVI) was readily alkylated by triethyloxonium borofluoride and diethyl sulfate. We were able to obtain the starting borofluoride (XVIII, $X = \text{BF}_4$).

To determine the structure of the new compounds that were prepared, we investigated the infrared and, in some cases, the ultraviolet absorption spectra. The infrared absorption spectra were determined in an IKS-12 apparatus with a prism of rock salt using suspensions in paraffin oil or solutions in chloroform. The ultraviolet spectra were determined in an SF-4 apparatus. The shifts observed in the absorption maxima for the derivatives of dimedone [2, 7] were also related fully to the derivatives of 5-phenylcyclohexanedione-1,3.

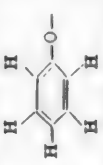
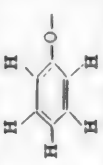
In the ultraviolet absorption spectrum of 5-phenylcyclohexanedione-1,3 in alkaline medium a maximum appeared at $282 \text{ m}\mu$, ϵ 15 300, characteristic of all the cyclohexanediones-1,3 [10], which characterizes the enolate anion form. But the phenylidone was characterized by a maximum at $261 \text{ m}\mu$, ϵ 11 600 (iodone $260 \text{ m}\mu$, ϵ 16 500), and the corresponding pyridinium enolate-betaine (XIV) by maxima at $252 \text{ m}\mu$, ϵ 16 400, and $361 \text{ m}\mu$, ϵ 550 [dimedone derivative (XVI) $260 \text{ m}\mu$, ϵ 19 150, and $366 \text{ m}\mu$, ϵ 1790], in spite of which both compounds undoubtedly exist in the enolate anion form.

In acid medium some hypsochromic shift of the maximum was observed for dimedone derivatives (about $10 \text{ m}\mu$), which is associated with the formation of un-ionized forms. In the case of the derivatives of 5-phenylcyclohexanedione-1,3, only a slight shift was observed. The decrease in the intensity of light absorption is possibly associated with decomposition of the material. N-(5-Phenylcyclohexanedion-1,3-yl-2)pyridinium borofluoride was characterized by a maximum at $253 \text{ m}\mu$, ϵ 19 350.

The infrared absorption spectra were more characteristic in the double bond region. The enolate anion system of dimedone was characterized by an extremely intense absorption in the region $1510\text{--}1530 \text{ cm}^{-1}$ and by some absorption at about $1560\text{--}1570 \text{ cm}^{-1}$ [7]. The sodium salt of 5-phenylcyclohexanedione-1,3 absorbed intensely at 1520 cm^{-1} and less intensely at 1579 cm^{-1} . The silver salt of 2-iodo-5-phenylcyclohexanedione-1,3 absorbed intensely in the region $1450\text{--}1490 \text{ cm}^{-1}$. Consequently, the enolate anion system of 5-phenylcyclohexanedione-1,3 absorbs similarly to the enolate anion of dimedone. The extremely intense absorption in the region of 1500 cm^{-1} apparently is explained by the vibrations of greatly deformed $\text{C}=\text{C}$ and $\text{C}=\text{O}$ double bonds in the symmetrical enolate anion system, which can be expressed by the formula (XIX, $R = \text{H}$), where $\delta \gg \delta'$ [11].



In the literature there are indications of absorption in the near region of the anions of malonic ester (1666 cm^{-1}), acetoacetic ester (1662 cm^{-1}), and acetylacetone (1604 cm^{-1}) [12]: Only one band is observed with an elevated frequency in comparison with the cyclohexanedione-1,3 system.

Origin of band		Characteristic absorption bands, cm ⁻¹ *					
Phenyl ether of the enol form			$\text{C}=\text{O}-\text{C}=\text{O}$	$\text{C}=\text{C}$ of phenoxy group	$\text{C}=\text{C}$ of enol	$\text{C}=\text{O}$	
Dimedone	—	697 (97), 771 (95), 792 (93)	1196 (100)	1485 (99), 1589 (85),**	1610 (95)**	1654 (88)**	
2-Iododimedone	—	689 (88), 763 (94), 797 (58)	1233 (99)	1482 (87), 1604 (83)	1585 (98)	1660 (98)	
5-Phenylcyclohexanedione-1,3	691 (66), 700 (59)	759 (64), 768 (85), 797 (55)	1205 (94)	1489 (80), 1589 (78)	1618 (86)	1659 (84)	
2-Iodo-5-phenylcyclohexanedione-1,3	695 (87)	759 (72), 772 (76)	1211 (100)	1600 (77)	1575 (98)	1657 (88)	
2,5-Diphenylcyclohexanedione-1,3	697 (82)	754 (53), 766 (61)	—	1486 (63), 1591 (79)	1628 (73)	1662 (90)	

• Percent absorption is indicated in parentheses.

•• The intensity is indicated for a suspension of lower concentration. In the suspension of the initial concentration in the given region only a broad band with an intensity of 100% was observed.

Obviously the absorption of the enolate anion system depends greatly on the distribution of the electron density in it. A clear example of this is the enolate-betaines of dimedone and 5-phenylcyclohexanedione-1,3 which were investigated. The phenyliodonium in chloroform solution absorbed at 1564 cm⁻¹, the iodonium at 1568 cm⁻¹, the pyridinium betaine (XIV) at 1546 cm⁻¹, and the dimedone derivative (XVI) at 1539 cm⁻¹. Consequently, a shift takes place in the main absorption band of the enolate anion in the direction of higher frequencies. This phenomenon is caused by the redistribution of the electron density in the direction of the carbon atom under the influence of the positively charged substituent. This same cause elicits the shift of the absorption maximum in the ultraviolet spectra.

In reflecting the structure of the enolate anions (XIX) it must be kept in mind that the ratios of the partial, localized charges δ and δ' may be different depending on the structure of the β -dicarbonyl compound, the nature of the substituent, and also the medium (solid state or various solvents), but $2\delta + \delta' = 1$ [13].

In the case of the phenyliodonium in the solid state the enolate anion system is destroyed, since absorption is observed at about 1606 cm⁻¹, which may be caused by dimerization [14].

The infrared spectra of the other compounds prepared also were investigated, in particular those of the iodonium salts of 5-phenylcyclohexanedione-1,3, the pyridinium derivatives of 5-phenylcyclohexanedione-1,3 and dimedone, and the phenyl ethers of the enol forms of 5-phenylcyclohexanedione-1,3 and dimedone.

In all the derivatives of 5-phenylcyclohexanedione-1,3 studied, frequencies of extraplanar vibrations of the five hydrogen atoms of the phenyl group appeared in the ranges 690-710 and 750-772 cm⁻¹. In the iodonium derivatives such vibrations of the C₆H₅I⁺ group appear in the ranges 675-678 and 722-744 cm⁻¹.

The vibrations of the five hydrogen atoms of the pyridinium ring appear in the ranges 672-688 and 769-789 cm⁻¹. For some pyridinium derivatives absorption appears in the range 986-994 cm⁻¹.

In the enol ether derivatives the absorption of the aliphatic ether grouping appears in the range 1038-1058 cm⁻¹, and especially intense absorption of the phenyl ethers appears in the range 1196-1233 cm⁻¹. In the boron fluorides the absorption is masked by the very intense band of the B-F bonds at about 1040-1080 cm⁻¹.

In the region of double bonds, as usual, vibrations of the carbonyl groups appeared in the range 1620-1662 cm⁻¹, those of the enol double bond in the range 1543-1628 cm⁻¹ (with the exclusion of the enolate anion derivatives),

and also the vibrations of the double bonds of the phenyl ring ($1482-1489$ and $1589-1591\text{ cm}^{-1}$) and the pyridinium ring ($1599-1629\text{ cm}^{-1}$). Definite interpretation of the bands in the region $1580-1630\text{ cm}^{-1}$ of the enol double bond and the aromatic rings presented difficulties. The interpretation presented in the table is based on comparison of the shifts of the frequencies of the enol double bond under the influence of the iodine substituent.

In the case of the pyridinium derivatives consolidation of the bands of the double bonds into one band was often observed.

The absorption of the pyridinium derivatives in the region $3030-3110\text{ cm}^{-1}$, which characterizes the vibration of the $=C-H$ bond, is interesting. These frequencies are high in comparison with the ordinary pyridine derivatives. Thus, the infrared spectra fully confirm the structure accepted for the compounds prepared [15].

EXPERIMENTAL

Phenyl-(5-phenylcyclohexanedione-1,3-yl-2)iodone (II). Nine and four tenths grams of 5-phenylcyclohexanedione-1,3 was suspended in 30 ml of chloroform, and 16.1 g of finely ground phenyl iodosoacetate, prepared by the method of Fox and Pausaker [16], was added gradually. A yellow solution was obtained, which was slowly diluted with 150 ml of ether. The solution gradually thickened to a white mass, which was filtered after 12 hours and washed well with ether. It was dried in vacuum over potassium hydroxide. Sixteen grams (82%) of the phenyliodone was obtained with m.p. 134° . The material was sufficiently pure for all further conversions.

The compound was crystallized from anhydrous alcohol in the form of colorless, very thin, long needles. M.p. $139-140^\circ$ (decomp.). The phenyliodone was moderately soluble in cold alcohols and chloroform, readily so in the hot solvents, slightly soluble in water, and insoluble in ether.

Found %: I 32.99. $C_{18}H_{15}O_2I$. Calculated %: I 32.52.

IR spectrum* (solid material): 696 (94), 755 (86, phenyl), 676 (83), 722 (96), 992 (82, iodonium system), 1530 (100, enol $C=C$), 1606 (97, carbonyl) cm^{-1} .

2-Chloro-5-phenylcyclohexanedione-1,3 (III). Nine tenths gram of the phenyliodone was covered with 3 ml of concentrated hydrochloric acid. The mixture was heated and a yellowish, semicrystalline material was formed, which was filtered off, washed with water, and treated with a solution of potassium hydroxide and with ether. After the ether layer had been removed, the solution was filtered and acidified. Forty-four hundredths gram (86%) of 2-chloro-5-phenylcyclohexanedione-1,3 was isolated with m.p. $194-195^\circ$. The compound was crystallized from acetic acid in the form of lustrous leaflets with m.p. $198-199^\circ$.

Found %: Cl 16.09. $C_{12}H_{11}O_2Cl$. Calculated %: Cl 15.95.

1-Iodo-2-phenoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -one-6 (IV). Three and nine tenths grams of the phenyliodone and 10 ml of pyridine were boiled for 15 minutes, diluted with 100 ml of water, and the pyridine and iodobenzene were steam distilled off. The residue, a brown semicrystalline mass, was crystallized from 10 ml of acetic acid. One and one tenth grams (28%) of slightly brownish crystals were obtained with m.p. $153-155^\circ$.

Found %: I 33.06. $C_{18}H_{15}O_2I$. Calculated %: I 32.52.

2-Phenoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -one-6 (V). One gram of compound (IV) was boiled with 10 ml of acetic acid and 5 g of zinc dust for 1 hour. The solution was filtered and diluted with 50 ml of water. The emulsion that formed gradually crystallized. Yield 0.48 g (67%). M.p. $94-96^\circ$. From dilute alcohol the 2-phenoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -one-6 crystallized in the form of colorless needles with m.p. $102-104^\circ$.

Found %: C 82.33; H 6.15. $C_{18}H_{16}O_2$. Calculated %: C 81.82; H 6.07.

Twenty-six hundredths gram of 2-phenoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -one-6 was dissolved in 2 ml of methanol, and 3-4 drops of concentrated hydrochloric acid were added. In a week the solution was diluted with water and filtered. The precipitate was dissolved in alkali, filtered, and acidified. Thirteen hundredths gram (69%) of 5-phenylcyclohexanedione-1,3 was isolated with m.p. $188-189^\circ$. A mixture with a known sample gave no depression in melting point.

*The present absorption and the structures to which the frequencies relate are given in parentheses.

From the filtrate 0.18 g (55%) of tribromophenol with m.p. 84- 6° was precipitated with bromine water. After recrystallization a mixture of the product with a known sample gave no depression in melting point.

Decomposition of the phenyliodone in the presence of pyridine and silver nitrate. One and ninety-five hundredths grams of the phenyliodone was dissolved in 5 ml of hot methanol and poured into a hot solution of 1.6 g of pyridine and 3.36 g of silver nitrate in 15 ml of water and heated for 5 minutes. The gray precipitate that separated out was filtered and washed with methanol. The yield of the silver salt of 2-iodo-5-phenylcyclohexanedione-1,3 (VI) was 1.92 g (91%). The compound was slightly soluble in water and alcohols and darkened on standing.

IR spectrum: 695 (84), 760 (67, phenyl), 1480 (100, enolate anion) cm^{-1} .

As evidence of the structure of the compound, 0.84 g of the silver salt (VI) was boiled with 10 ml of 1 N alkali solution, filtered from the silver oxide that was formed, and the filtrate acidified. Yield 0.55 g (88%) of 2-iodo-5-phenylcyclohexanedione-1,3 (VIII) with m.p. 164-165°. The recrystallized compound melted at 172°. A mixture with 2-iodo-5-phenylcyclohexanedione-1,3 prepared by iodination of 5-phenylcyclohexanedione-1,3 gave no depression in melting point.

1-Iodo-2-ethoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -one-6 (VII). Eighty-four hundredths gram of the silver salt (VI) was boiled with 5 ml of ethyl iodide for 2 hours. The precipitate that formed was treated with 35 ml of hot alcohol. On cooling, lustrous leaflets of compound (VII) precipitated. Yield 0.37 g (58%). M.p. 155°. The compound decomposed on standing.

Found %: I 37.57. $\text{C}_{14}\text{H}_{15}\text{O}_2\text{I}$. Calculated %: I 37.13.

IR spectrum: 698 (58), 765 (39, phenyl), 1048 (70, C-O bond), 1567 (100, C=C bond), 1645 (94, C=O) cm^{-1} .

Phenylation of 5-phenylcyclohexanedione-1,3. Nine and four tenths grams of 5-phenylcyclohexanedione-1,3 was dissolved in a mixture of 30 ml of water, 30 ml of dioxane, and 2 g of sodium hydroxide, and 18 g of diphenyliodonium bromide was added gradually at boiling. The mixture was boiled for 3 hours; then the iodobenzene that had formed was steam distilled off. Eleven and five tenths grams of a brownish material was obtained, which was triturated and treated with alkali solution. From the alkaline filtrate a colorless precipitate was obtained by acidification, and was crystallized from alcohol. Six tenths gram of 2,5-diphenylcyclohexanedione-1,3 (IX) was obtained with m.p. 236-239°. After recrystallization from acetic acid the m.p. was 242-243°; according to the data in the literature the m.p. is 247-249° [17].

The mass which was insoluble in alkali was treated with methanol and filtered. Seven tenths gram of a colorless powder was obtained with m.p. 140-143°, which was crystallized from alcohol. 2-Phenoxy-1,4-diphenylcyclohexan- $\Delta^{1,2}$ -one-6 (X) crystallized in the form of long needles with m.p. 144-145°.

Found %: C 84.70, 84.20; H 5.99, 6.07. $\text{C}_{24}\text{H}_{20}\text{O}_2$. Calculated %: C 84.71; H 5.88.

Fourth-three hundredths gram of compound (X) was dissolved with heating in 5 ml of acetic acid and 1 ml of concentrated hydrochloric acid was added. Lustrous leaflets gradually separated out. The mixture was diluted with water and filtered. Thirty-one hundredths gram (94%) of 2,5-diphenylcyclohexanedione-1,3 was obtained with m.p. 233-240°. A mixture with the sample obtained above gave no depression in melting point. From the filtrate 0.37 g (88%) of tribromophenol was precipitated with bromine water.

Phenyl-(2-benzoyloxy-4-phenylcyclohexan- $\Delta^{1,2}$ -one-6-yl-1)iodonium bromide (XI, X = Br). To one and six tenths grams of the phenyliodone was added 2 ml of benzoyl chloride, and after 1 hour 30 ml of absolute ether was added and the mixture was stirred well. It was filtered and washed with ether. Ninety-six hundredths gram of a colorless powder was obtained with m.p. 64° (decomp.). The product was dissolved in 8 ml of methanol, and an aqueous solution of potassium bromide was added. The precipitate was filtered off and dried. Yield 0.76 g, m.p. 67° (decomp.). The compound was purified by reprecipitation from methanol with ether. Colorless powder. M.p. 85-87° (decomp.).

Found %: I 22.58. $\text{C}_{25}\text{H}_{20}\text{O}_3\text{BrI}$. Calculated %: I 22.08.

IR spectrum: 679 (83), 785 (27, phenyl), 676 (61), 733 (54), 991 (59, iodonium system), 1018 (86), 1043 (82, C-O bond), 1601 (85, C=C bond), 1676 (76, C=O bond), 1747 (86, benzoyl C=O) cm^{-1} .

Phenyl-(2-ethoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -on-6-yl-1)iodonium borofluoride (XII, X = BF_4). To triethyloxonium borofluoride, prepared as described by Meerwein [18] from 5.7 g of boron trifluoride etherate and 4.2 g of

epichlorohydrin, was added 20 ml of chloroform, then 9.73 g of the phenyliodone, and the mixture was boiled until a homogeneous solution was formed and then was cooled. Two ml of alcohol and 50 ml of ether were added and the mixture was shaken vigorously. A thick oil formed, which stuck to the walls of the container. The ether was poured off, and the remainder of the ether was removed in vacuum. About 11 g of a thick mass was obtained, which was purified by dissolving it in 30 ml of anhydrous alcohol and precipitating with 90 ml of absolute ether. About 7 g of a thick mass was obtained which was used for the further reactions. For analysis, this material was again precipitated from alcohol with ether and carefully dried in vacuum. Colorless amorphous powder with m.p. 55-70°.

Found %: I 25.41. $C_{20}H_{20}O_2BF_4I$. Calculated %: I 25.10.

IR spectrum: 699 (56), 765 (43, phenyl), 675 (50), 739 (57), 986 (74, iodonium system), 1044 (87, C-O and B-F bond), 1551 (90, C=C bond), 1656 (68, C=O bond) cm^{-1} .

Phenyl-(2-ethoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -on-6-yl-1)iodonium bromide (XII, X = Br). Four tenths gram of the borofluoride (XII, X = BF_4) was dissolved in 5 ml of methanol, and at 0° 50 ml of an aqueous solution of potassium bromide was added. After several hours the mixture was filtered. Yield 0.34 g of colorless powder with m.p. 133-135° (decomp.). It was crystallized from 3 ml of anhydrous alcohol. Yellowish crystals gradually separated out. M.p. 140-141° (decomp.).

Found %: I 25.54. $C_{20}H_{20}O_2BrI$. Calculated %: I 25.45.

IR spectrum: 701 (42), 765 (28, phenyl), 677 (39), 744 (37), 989 (24, iodonium system), 1038 (39, C-O bond), 1543 (94, C=C bond), 1620 (68, C=O bond) cm^{-1} .

N-(2-Ethoxy-4-phenylcyclohexan- $\Delta^{1,2}$ -on-6-yl-1)pyridinium borofluoride (XIII). To six and four tenths grams of the borofluoride (XII, X = BF_4) was added 10 ml of anhydrous pyridine. The mixture was heated and a homogeneous solution gradually formed. After several hours the solution was diluted with 100 ml of ether and was vigorously shaken. The ether was poured off, and the remainder of the ether was removed in vacuum from the oil that had separated out. Four grams of a semicrystalline mass was obtained, which was crystallized from 40 ml of alcohol. Colorless needles with m.p. 168-170°. Yield 2.4 g (50%). After repeated crystallization the m.p. was 170-171°.

Found %: N 6.32; BF_4^- 22.51. $C_{19}H_{20}O_2NBF_4$. Calculated %: N 3.68; BF_4^- 22.83.

IR spectrum: 703 (72), 769 (75, phenyl), 680 (76), 786 (30, pyridinium), 1045-1078 (100, C-O and B-F bonds), 1613 (100, double bonds of enol and pyridinium), 1662 (97, C=O), 3058 and 3110 (C-H of pyridinium) cm^{-1} .

N-(5-Phenylcyclohexanedion-1,3-yl-2-)pyridinium enolate-betaine (XIV). a) To one and fifty-two hundredths grams of the borofluoride (XIII) was added 30 ml of water, then 2 ml of concentrated hydrochloric acid, and the mixture boiled for 45 minutes. Two grams of sodium hydroxide was added. Yellow crystals gradually separated out. Yield 0.68 g (57%) with m.p. 202-204°. After repeated crystallization from water the melting point did not change. The compound crystallized with 2 molecules of water.

b) Five tenths gram of 2-bromo-5-phenylcyclohexanedione-1,3 was boiled for 15 minutes with 5 ml of pyridine. The mixture was cooled and 25 ml of ether was added. The precipitate was filtered off and crystallized from water. Yield 0.24 g (45%) of yellow material with m.p. 202-204°.

Found %: N 4.62; H_2O 12.26. $C_{17}H_{15}O_2N \cdot 2H_2O$. Calculated %: N 4.65; H_2O 11.98.

The anhydrous compound was a dark yellow powder with m.p. 202-204°.

Found %: N 5.33. $C_{17}H_{15}O_2N$. Calculated %: N 5.28.

IR spectrum: 699 (71), 765 (81, phenyl), 676 (74), 686 (81), 784 (58, pyridinium), 1530 (100, enolate anion), 1602 (64, pyridinium double bond), 3030 and 3110 (C-H bonds of pyridinium) cm^{-1} .

The perchlorate of the enolate-betaine was obtained by crystallization of the compound from dilute perchloric acid. Colorless crystals with m.p. 250-251° (decomp.).

Found %: N 3.64. $C_{18}H_{16}O_6NCl$. Calculated %: N 3.83.

IR spectrum: 703 (61), 764 (78, phenyl), 679 (81), 779 (50, pyridinium), 1032 (98), 1125 (96, ClO_4), 1603 (51), 1622 (77, double bonds of enol and pyridinium), 1661 (100, C=O), 3054 (C-H bonds of pyridinium) cm^{-1} .

N-(2-Ethoxy-4,4-dimethylcyclohexan- $\Delta^{1,2}$ -on-6-yl-1) borofluoride (XVIII, X = BF₄). Twenty-one and nine tenths grams of the borofluoride (XVII) was stirred with 15 ml of pyridine at 20° for 10 hours; the crystals were separated off and washed with alcohol and ether. Yield 13 g (73%). M.p. 134-140° (at 120° there was partial melting). In some other experiments we obtained crystals which melted completely at 120°. After crystallization from alcohol the m.p. was 120-121°. Colorless prismatic crystals.

Found %: N 5.38, 5.75, 4.95; BF₄⁻ 25.85. C₁₅H₂₀O₂NBF₄. Calculated %: N 4.20; BF₄⁻ 26.13.

IR spectrum: 686 (81), 776 (47), 712 (39, pyridinium), 1033-1069 (100, C-O and B-F bonds), 1616 (95, double bonds of enol and pyridinium), 1662 (85, C=O), 3040 and 3096 (C-H bonds of pyridinium) cm⁻¹.

The perchlorate (XVIII, X = ClO₄) was isolated from aqueous solutions of the borofluoride after the addition of perchloric acid in the form of a less soluble precipitate. Crystals with m.p. 140-141°.

Found %: N 5.32, 4.93, 5.48; ClO₄⁻ 28.47. C₁₅H₂₀O₂NCl. Calculated %: N 4.05; ClO₄⁻ 28.80.

IR spectrum: 682 (79), 775 (85), 710 (39, pyridinium), 1058 (98, C-O bond), 1077-1107 (100, ClO₄), 1614 (100), 1625 (93, double bonds of enol and pyridinium), 1658 (95, C=O), 3060 and 3110 (C-H bonds of pyridinium) cm⁻¹.

N-(Dimedonyl-2)pyridinium enolate-betaine (XVI). Ten grams of the borofluoride (XVIII, X = BF₄) was wet with 5 ml of concentrated hydrochloric acid and heated on a boiling water bath for 3 hours. The mixture was cooled, 10 ml of water and 10 g of potassium carbonate were added, and all was shaken with dichloroethane or chloroform (twice with 200-ml portions). After the solvent had been distilled off, 5.5 g (85%) of yellow needles was obtained. M.p. 194-196°. After crystallization from a mixture of anhydrous alcohol and ether, the betaine melted at 197-198°.

Found %: N 6.64, 6.39. C₁₃H₁₅O₂N. Calculated %: N 6.45.

IR spectrum: 688 (59), 789 (55, pyridinium), 1544 (100, enolate anion), 1600 (40), 1620 (32, double bonds of pyridinium), 3050 and 3100 (C-H bonds of pyridinium) cm⁻¹.

When the betaine was recrystallized from a mixture of alcohol and moist ether, the dihydrate was obtained in the form of light yellow needles. M.p. 88-90°.

Found %: N 5.39, 6.05. C₁₃H₁₅O₂N · 2H₂O. Calculated %: N 5.53.

The perchlorate was obtained by adding perchloric acid to an aqueous solution of the betaine. From a mixture of anhydrous alcohol and ether the compound crystallized in the form of light yellow prisms. M.p. 182-184°.

Found %: N 4.93. C₁₃H₁₅O₆NCl. Calculated %: N 4.41.

IR spectrum: 682 (74), 777 (58, pyridinium), 1090-1110 (100, ClO₄), 1619 (75), 1629 (80, double bonds of enol and pyridinium), 1655 (72, C=O), 3045 and 3100 (C-H bonds of pyridinium) cm⁻¹.

SUMMARY

1. 5-Phenylcyclohexanedione-1,3 reacts easily with phenyl iodosoacetate to form an iodonium compound of the enolate-betaine type - a phenyliodone.

2. The phenyliodone is capable of cleavage with the rupture of the carbon-iodine bond in two directions depending on the nature of the attacking reagent.

3. The phenyliodone is easily acylated and alkylated, forming iodonium salts that are difficult to crystallize and slightly stable.

4. The iodonium salts of the 5-phenylcyclohexanedione-1,3 series and of dimedone are easily cleaved in the presence of pyridine, with the formation of the corresponding pyridinium derivatives.

5. The enolate-betaines of 5-phenylcyclohexanedione-1,3 and of dimedone which were prepared were investigated by spectral methods, and the relationship of the fine structure of the enolate anions to structural factors was shown.

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BIS(β -CHLOROETHYL)AMINES OF BICYCLIC COMPOUNDS

IV. THE PREPARATION OF BENZO- AND METHOXYBENZOCYCLOHEPTYLAMINES-5 AND SOME OF THEIR DERIVATIVES

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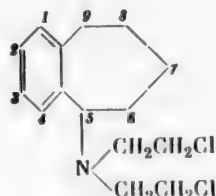
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The present communication concerns the synthesis of N-dichlorodiethyl derivatives of benzo- and methoxybenzocycloheptylamines-5 for the purpose of investigating their biological properties.



The synthesis of these compounds was carried out by a scheme adopted by us for the preparation of bis(β -chloroethyl)amines of the indan series [1]: By the cyclization of aliphatic-aromatic acids, in this case phenylvaleric acids or their acid chlorides, bicyclic ketones are obtained, the oximes of which are reduced with the aid of lithium aluminum hydride or aluminum amalgam to amines; from the latter the bis- β -hydroxyethyl derivatives are prepared, and then the hydroxyls are replaced by chlorine atoms.

We prepared δ -(*m*-methoxyphenyl)valeric acid, which has not been described in the literature, by the conversion of the condensation product of *m*-methoxybenzaldehyde with the diester of ethylenemalononic acid as recommended [2] for the preparation of the isomeric *o*- and *p*-methoxyphenylvaleric acids.

Cyclization of the phenyl- and methoxyphenylvaleric acids was carried out with the aid of polyphosphoric acid or under the conditions of the Friedel-Crafts reaction. The formation of the seven-membered ring took place with more difficulty than the cyclization of phenylpropionic acids to compounds with a five-membered ring. When *m*-methoxyphenylvaleric acid was cyclized, which can take place in both the ortho and the para position in the benzene ring with relation to the methoxy group, we isolated only one ketone, while when *m*-methoxyphenylpropionic acid is cyclized, two ketones are formed [2], and moreover the predominant direction of the reaction is closing of the ring in the position para to the methoxy group.

We did not determine the structure of the ketone which we isolated; however, the data on the cyclization of *m*-methoxyphenylpropionic acid permit the assumption by analogy that the cyclization of *m*-methoxyphenylvaleric acid took place in the position para to the methoxy group, and that the ketone isolated by us was 2-methoxycycloheptanone-5.

Like other investigators [2], we were not able to cyclize *p*-methoxyphenylvaleric acid. It is pertinent to recall that it is possible to carry out a similar reaction with *p*-methoxyphenylpropionic acid by selecting certain conditions, and to obtain the corresponding ketone in good yield.

The preparation from bicyclic amines of their hydroxyethyl and chloroethyl derivatives was carried out under the usual conditions, and 5-bis(δ -chloroethyl)aminobenzocycloheptane was isolated in the form of the hydrochloride.

From 2-methoxy-5-aminobenzocycloheptane we were able to obtain only the dihydroxyethyl derivative; experiments on the replacement of the hydroxy groups with chlorine were unsuccessful, since cleavage of the molecule occurred and di(δ -chloroethyl)amine was produced.

EXPERIMENTAL

5-Aminobenzocycloheptane (I). a) To 5.27 g of lithium aluminum hydride, suspended in 118 ml of absolute ether, was added with stirring a solution of 5.43 g of the oxime of benzocycloheptanone-5 [4] with m.p. 108-109°

in a mixture of 79 ml of absolute ether and 33 ml of anhydrous benzene, and the mixture was heated at boiling for 7 hours. Then the reaction mixture was cooled and 21 ml of water was added dropwise at such a rate that quiet boiling was maintained. The mixture was filtered, the ether was distilled off, and the residue was distilled in vacuum. Yield 4.3 g (78%), b.p. 100-106° at 3-5 mm.

b) To 15 g of aluminum amalgam in 100 ml of absolute ether was added 3.5 g of the oxime of benzocycloheptanone-5 in 50 ml of absolute ether. The reaction mixture was heated at boiling for 30 minutes, and 40 ml of water was added dropwise in the course of 9 hours. The ether layer was separated and dried; the ether was removed, and the residue was distilled in vacuum. B.p. 133-136° at 13-14 mm; 142-143° at 22-23 mm; the material avidly absorbed carbon dioxide.

The hydrochloride of 5-aminobenzocycloheptane formed colorless crystals from anhydrous alcohol on the addition of a small amount of ether; m.p. 267-270° (decomp.).

Found %: C 66.85; H 8.35; Cl 18.45. $C_{11}H_{15}N \cdot HCl$. Calculated %: C 66.83; H 8.10; Cl 17.97.

5-Bis(β -hydroxyethyl)aminobenzocycloheptane (I). A mixture of 11.5 g of 5-aminobenzocycloheptane (I) and 7.5 ml of ethylene oxide was heated in a sealed tube for 4-5 hours at 130-140°. A thick oily material was obtained, which was readily soluble in benzene, chloroform, alcohol, and more difficultly soluble in ether. B.p. 240-250° at 15-17 mm. Yield 15 g (84.5%).

The hydrochloride of 5-bis(β -hydroxyethyl)aminobenzocycloheptane was a colorless crystalline powder, soluble in alcohol and in water, insoluble in ether; m.p. 111-112° (from alcohol).

Found %: C 62.67; H 8.38; N 4.85; Cl 12.30. $C_{18}H_{25}O_2N \cdot HCl$. Calculated %: C 63.00; H 8.40; N 4.90; Cl 12.43.

5-Bis(β -chloroethyl)aminobenzocycloheptane hydrochloride (III). A mixture of 26.8 g of the amine (II), 25 ml of anhydrous chloroform, and 46 ml of thionyl chloride was stirred at room temperature for 3 hours and then left to stand overnight. The solvent and the excess thionyl chloride were removed. The residue was washed with absolute ether and crystallized from an anhydrous mixture of benzene and alcohol; m.p. 147.5-148.5°.

Found %: C 55.90; H 6.76; N 4.36; Cl 33.10. $C_{18}H_{21}NCl_2 \cdot HCl$. Calculated %: C 55.81; H 6.82; N 4.34; Cl 33.02.

δ -(p-Methoxyphenyl)valeric acid. δ -(p-Methoxyphenyl)valeric acid, which has been described in the literature [5, 6], was prepared by us by the reduction by Clemmensen's method of anisoylbutyric acid, which is easily produced by condensation of anisole with glutaric anhydride [7].

A mixture consisting of 16 g of γ -(p-methoxybenzoyl)butyric acid, amalgamated zinc from 75 g of granulated zinc, 7.5 g of mercuric chloride in 125 ml of water, 110 ml of toluene, 110 ml of glacial acetic acid, and 110 ml of concentrated hydrochloric acid was heated at boiling for 36 hours, with the addition every 3-4 hours of 10-15 ml of concentrated hydrochloric acid. After the usual treatment, 13 g of the acid was obtained with m.p. 113-114°.

δ -(p-Methoxyphenyl)valeryl chloride was prepared by heating the acid with thionyl chloride in chloroform solution; b.p. 143-145° at 3 mm.

Found %: C 63.35; H 6.68; Cl 15.49. $C_{12}H_{15}O_2Cl$. Calculated %: C 63.66; H 6.62; Cl 15.67.

m-Methoxycinnamylidenemalonic acid. Three and four tenths grams of m-methoxybenzaldehyde was gradually added to 8 g of diethyl ester of ethylidenemalonic acid in 17 ml of anhydrous alcohol. To the mixture obtained was added dropwise with stirring 26 ml of 50% choline solution in anhydrous methanol. Slight warming of the mixture was observed (35-40°). The reaction mixture was stirred until it cooled to room temperature and then left to stand for 48 hours. After this time the solution took on a red color. To it was added 120 ml of water, and the mixture obtained was refluxed on a water bath for 1 hour. Upon cooling, 40 ml of dilute hydrochloric acid (1:1) was added and the mixture was left to stand overnight at 5°. The yellow precipitate that separated out was recrystallized from methanol. Five and five tenths grams (88.6%) of dicarboxylic acid was obtained with m.p. 200-201°.

Found %: C 63.05; H 4.96. $C_{13}H_{12}O_5$. Calculated %: C 62.90; H 4.84.

δ -(m-Methoxyphenyl)valeric acid (IV). Ten grams of m-methoxycinnamylidenemalonic acid was dissolved in 500 ml of alcohol, and the solution obtained was shaken with 0.5 g of platinum oxide in a hydrogen atmosphere at

room temperature. The theoretically necessary amount of hydrogen was absorbed in 15-20 minutes. The catalyst was filtered off and the solvent was removed in vacuum. An oily material remained, which lost CO_2 both on distillation in vacuum and on heating for 5 hours with 10 times its amount of anhydrous pyridine. Six and five tenths grams (77.7%) of δ -(*m*-methoxyphenyl)valeric acid was obtained with b.p. 170-175° at 2 mm.

Found %: C 69.35; H 7.55. $\text{C}_{12}\text{H}_{16}\text{O}_3$. Calculated %: C 69.20; H 7.69.

2-Methoxybenzocycloheptanone-5 (V). To the polyphosphoric acid prepared from 144 ml of phosphoric acid and 216 g of P_2O_5 was added 15 g of the acid (IV) at 70° with stirring. The mixture obtained was stirred at the same temperature for another 30 minutes, then was cooled and poured into such an amount of 15% sodium carbonate solution that the reaction of the newly obtained mixture was weakly alkaline. On standing, an oily material separated out, which gradually solidified. After recrystallization of it from alcohol, 11 g of material was obtained with m.p. 54-56°.

Found %: C 75.62; H 7.41. $\text{C}_{12}\text{H}_{14}\text{O}_2$. Calculated %: C 75.78; H 7.37.

2-Methoxybenzocycloheptanone-5 oxime (VI). To a solution of 11.3 g of the ketone (V) in 500 ml of alcohol was added with stirring 4.73 g of hydroxylamine hydrochloride; after the addition of the salt, the mixture obtained was stirred without heating until the hydroxylamine salt had completely dissolved, with the gradual addition of 7.6 g of barium carbonate. The reaction mixture was heated at boiling for 5 hours. After the precipitate had been separated, the alcohol was partially removed and the remaining mixture diluted with water; the oxime which precipitated melted after recrystallization at 122-124°; yield 10.3 g (84.5%).

Found %: C 70.26, 70.25; H 7.45, 7.46; N 6.66, 6.52. $\text{C}_{12}\text{H}_{15}\text{O}_2\text{N}$. Calculated %: C 70.24; H 7.31; N 6.83.

2-Methoxy-5-aminobenzocycloheptane (VII). Ten and four tenths grams of the oxime (VI) dissolved in 450 ml of absolute ether was added to 40 g of amalgamated aluminum turnings. The mixture obtained was stirred at the boiling point of the ether for 30 minutes, after which 100 ml of water was added dropwise over the course of 8 hours with continuous boiling of the ether. The reaction mixture was left to stand overnight. After the usual treatment and distillation of the material in vacuum, 7.35 g of amine (VII) was obtained in the form of an oily material with b.p. 141-143° at 4-5 mm, which avidly absorbed CO_2 .

2-Methoxy-5-aminobenzocycloheptane hydrochloride was a colorless crystalline powder with m.p. 252-254° (from alcohol).

Found %: C 62.93; H 8.02; N 6.02; Cl 14.98. $\text{C}_{12}\text{H}_{17}\text{ON} \cdot \text{HCl}$. Calculated %: C 63.29; H 7.91; N 6.15; Cl 15.60.

2-Methoxy-5-bis(β -hydroxyethyl)aminobenzocycloheptane hydrochloride (VIII). Seven and four tenths grams of the amine (VII) and 4 ml of ethylene oxide were heated in a sealed tube for 4 hours at 140°. The reaction mixture obtained was dissolved in ether, and the ether solution was acidified with an ether solution of hydrogen chloride. A colorless crystalline material precipitated, which was soluble in water and alcohol; m.p. 125-130°.

Found %: C 60.18; H 8.03; N 4.46; Cl 11.12. $\text{C}_{16}\text{H}_{25}\text{O}_2\text{N} \cdot \text{HCl}$. Calculated %: C 60.85; H 8.26; N 4.43; Cl 11.20.

SUMMARY

1. 5-Bis(β -chloroethyl)aminobenzocycloheptane has been synthesized.
2. A series of compounds not described in the literature which are intermediate compounds in the synthesis of bis(β -chloroethyl)-aminobenzocycloheptane and its 2-methoxy derivatives has been prepared.
3. It has been established that in methoxy-5-(β -chloroethyl)aminobenzocycloheptane the bond between the nitrogen atoms and the carbon ring is not stable.

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ORGANOBORON COMPOUNDS

LXV. SYNTHESIS OF ESTERS OF DIALKYLTHIOBORIC ACIDS

BY THE ACTION OF MERCAPTANS ON TRIALKYL BORONS

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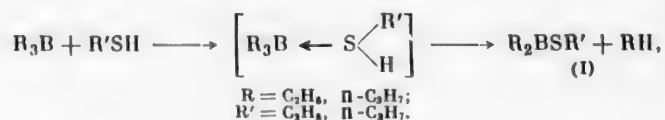
January, 1961

Original article submitted February 1, 1960

We have shown previously [1-3] that the reaction of the higher trialkylborons with compounds containing a labile hydrogen atom (water, alcohols, amines, *n*-butylmercaptan, thiophenol, hydrazine, and phenylhydrazine) is accompanied by the splitting out of a saturated hydrocarbon or a mixture of saturated and unsaturated hydrocarbons and hydrogen and the formation of the corresponding oxygen-, nitrogen-, or sulfur-containing organoboron compounds. Moreover, the reaction of the trialkyl borons with the mercaptans takes place the most readily, starting at room temperature and being accompanied by strong heating of the reaction mixture. The esters of dialkylthioboric acids obtained as a result of the reaction react with great ease with alcohols [4], amines [4], ammonia [4], hydrazine [4, 5], phenylhydrazine [4, 5], hydrogen sulfide [6], hydrocyanic acid [6], and *N*-phenyl-*N'*-dialkylborylhydrazine [5].

In this communication we present the results of an investigation of the reactions of trialkyl borons with ethyl mercaptan, *n*-propyl mercaptan, and thiophenol, the conversion of the esters of dialkylthioboric acids under the influence of alcohols, and also the reactions of trialkyl borons with alcohols in the presence of catalytic amounts of mercaptans.

When ethyl mercaptan or *n*-propyl mercaptan acts on triethyl- or tri-*n*-propylboron, the corresponding esters of the dialkylthioboric acids (I) and saturated hydrocarbons are formed. The reaction starts at room temperature and is accompanied by spontaneous heating; to complete the process, short heating of the reaction mixture at 110-160° is required.

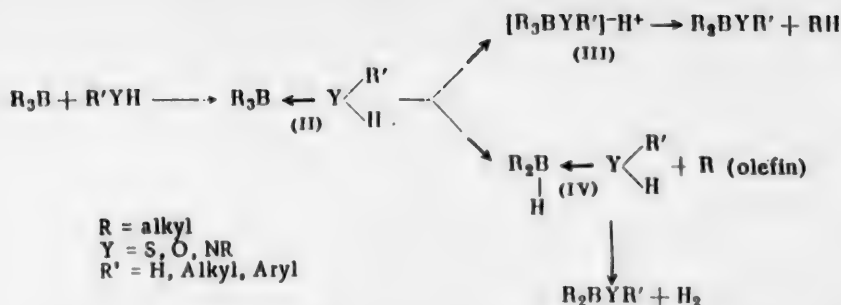


Carrying out the reaction by adding the mercaptan to the trialkyl borons heated to 150° leads to the formation of small amounts (up to 10%) of hydrogen and unsaturated hydrocarbon [1].

The reaction of thiophenol with tri-*n*-butyl boron, which leads to the formation of the phenyl ester of di-*n*-butylboric acid, proceeds in a manner similar to the reaction with tri-*n*-propyl boron [1]. It starts at a higher temperature (50°) and is accompanied by the formation not only of saturated hydrocarbon (*n*-butane), but also of slight amounts of hydrogen and unsaturated hydrocarbon (butene).



The formation of gaseous products of different composition in the reaction of the trialkyl borons and compounds with a labile hydrogen, in particular with the mercaptans and thiophenyl, is explained by the previously proposed mechanism for the course of the process [1]:



According to this mechanism, in the first stage of the reaction a complex compound of the trialkyl boron with some other addend (II) is formed. The further behavior of the complexes (II) is determined mainly by the nature of the addend and to a lesser extent by the size and structure of the hydrocarbon radicals attached to the boron atom.

In the complex compound of the trialkyl boron with a mercaptan the polarization of the donor-acceptor bond in the direction of the boron atom (II) occurs to such an extent that the complex proves to be capable of dissociating at room temperature. In the dissociated boronium acid that is formed (III), heterolytic rupture of the boron-carbon bond occurs and the carbonium ion, combining with a proton, forms a saturated hydrocarbon.

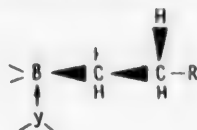
The easy rupture of the boron-carbon bond in the boronium acids has been observed in our laboratory repeatedly. Thus, when the lithium salt of diphenyldiisobutoxyboronium acid is acidified [7], the ester of phenylboric acid is predominantly formed; the diphenylarylisobutoxyboronium acid is converted to the ester of the diphenylboric acid [8], and the alkylphenylchloroboronium acids decompose with the formation of alkylboric acids along with alkylphenylboric acids [9].

In the complex of trialkyl boron with thiophenol the electronegative phenyl radical decreases the shift of the negative charge in the direction of the boron atom, as a result of which the tendency of the complex to dissociation with the formation of the boronium acid (III) is decreased. As a result of this the conversion of the complex takes place at a higher temperature, which promotes not only its dissociation and the subsequent conversion to the ester of the dialkylthioboric acid and saturated hydrocarbon, but also direct composition with the elimination of olefin hydrocarbon.

This second direction of the reaction, which leads in the final event also to the formation of the ester of the dialkylthioboric acid, unsaturated hydrocarbon, and hydrogen, is most clearly expressed in the conversions of the trialkyl borons with oxygen compounds (water, alcohols) and nitrogen compounds (amines, hydrazine) which have a labile hydrogen atom.

The oxygen and nitrogen-containing addends, which have more electronegative hetero atoms than the mercaptans, form complexes with the trialkyl borons with less polarized donor-acceptor bonds, as a result of which the capacity of such complexes for protonization is lowered still more than in the complexes with thiophenol. The complex compounds with oxygen and nitrogen addends undergo conversion only at 160-200°, and the prevailing direction of their decomposition is the elimination of olefin hydrocarbon.

Thanks to the inductive effect of the negatively charged boron atoms, polarization of the bonds in the hydrocarbon radical takes place, facilitating the splitting out of a hydride ion (H^-) from the β -carbon atom. This act, which is accompanied by heterolytic rupture of a boron-carbon bond and migration of the hydride ion to the boron atom, leads to the elimination of olefin hydrocarbon (the so-called β -decomposition of heteroorganic compounds) and the formation of a complex of the dialkylborane with the addend (IV).



The complexes of the dialkylboranes (IV) easily decompose with the evolution of hydrogen and the formation of compounds of the type R_2BYR' .

The process which we investigated of splitting out olefin hydrocarbon in reactions of the trialkyl borons with various compounds containing labile hydrogen is observed also when the individual trialkyl borons are heated [10]. It has been found [1] that the splitting out of olefins takes place more readily in complexes of compounds of the trialkyl borons with tertiary amines than in free trialkyl borons. Thus, the splitting out of butene when the pyridinate of tri-*n*-butyl boron is thermally decomposed (180°) is fully completed in 6 hours, while tri-*n*-butyl boron undergoes a similar conversion only as a result of ten days heating at the same temperature [10].

The process of elimination of olefins in the thermal decomposition of the trialkyl borons is affected by the structure of the radicals connected with the boron atom. From the data obtained previously [1] it follows that the alkyl groups can be arranged in the following order with respect to the ease of splitting out olefins, which can be judged by the ratio of the saturated and unsaturated hydrocarbons formed:



The arrangement of the alkyl groups in the indicated order is associated with the presence and the number of hydrocarbon radicals on the β -carbon atom, which because of their positive inductive effect facilitate the splitting off of the hydride ion (H^-) from the β -carbon atom.

When onium compounds, for example sulfonium [11], decompose, the reverse order is observed for the alkyl groups with respect to the ease of splitting out olefin, since in this case a proton is split off from the β -carbon atom, and the inductive effect of the radicals hinders this process.

The esters of the dialkylthioboric acids on heating with alcohols are converted to esters of dialkylboric acids. In this way it is possible to synthesize even the difficultly available methyl esters R_2BOCH_3 [4]. By heating the *n*-butyl ester of di-*n*-propylthioboric acid with *n*-butyl alcohol we prepared the *n*-butyl ester of di-*n*-propylboric acid.

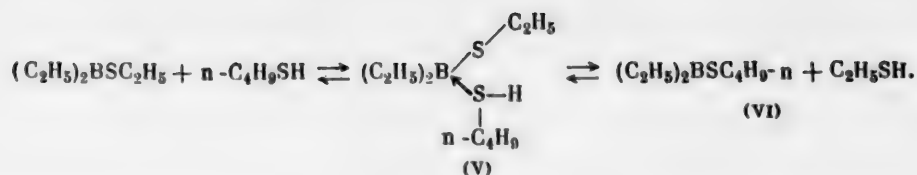


The process is not complicated by side reactions, as is the case in the alcoholysis of esters of di-2-(methyl-diethylsilylethyl)thioboric acid, where, as a result of cleavage of the boron-carbon bond, the ester of 2-methyl-diethylsilylethylboric acid is obtained as well as the ester of di-2-(methylethylsilylethyl)boric acid [12].

The tendency of the trialkyl borons to react with mercaptans at high temperature and the high reactivity of the esters of dialkylthioboric acids which are produced can be utilized for the synthesis of various compounds of the type R_2BYR' from trialkyl borons and compounds with a labile hydrogen under the influence of catalytic amounts of mercaptan.

At room temperature the trialkyl borons do not react with alcohols. When a small amount of mercaptan is added to the reaction mixture, however (about 0.1 equivalent), a vigorous reaction starts, which is accompanied by spontaneous heating and the separation of saturated hydrocarbon. As a result, the esters of the dialkylboric acids are obtained in high yields. The first stage of the process is the reaction of the trialkyl boron and the mercaptan, resulting in the formation of saturated hydrocarbon and the thioester R_2BSR' , which quickly reacts with the alcohol to produce the ester of the dialkylboric acid and regenerate the mercaptan. The mercaptan again enters into further reaction with the trialkyl boron and the process is repeated until all of the alcohol or the trialkyl boron is used up. Thus, by utilizing the catalytic action of *n*-butyl mercaptan, we synthesized the *n*-butyl ester of di-*n*-butylboric acid and the methyl ester of di-*n*-propylboric acid from the appropriate trialkylborons and alcohols.

With the higher mercaptans the esters of the dialkylboric acids enter into a transesterification reaction - "transmercaptanization". The course of this reaction probably depends on the formation of a complex between the mercaptan and the thioester (V), which exists in equilibrium with the starting compounds and the newly formed thioester (VI) and the mercaptan. As a result of the removal from the sphere of reaction of the low-boiling thiol, the equilibrium shifts to the right. Thus, from the ethyl ester of diethylboric acid and *n*-butyl mercaptan we obtained the *n*-butyl ester of diethylthioboric acid (VI).



EXPERIMENTAL *

Ethyl ester of diethylthioboric acid. The reaction was carried out in a three-necked flask fitted with a reflux condenser, dropping funnel, delivery tube for nitrogen, and thermometer and connected through the condenser with a gasometer. To 14.2 g of triethylboron was slowly added with stirring 14 ml of ethyl mercaptan. The reaction proceeded very vigorously, with strong evolution of heat. When the addition of the mercaptan had been completed, the reaction mass was heated for 10 minutes at 110°. The gas given off contained an equivalent of ethane. After fractional distillation in vacuum, we obtained 15.7 g (83.6%) of the ethyl ester of diethylthioboric acid, b.p. 89-90° at 100 mm, n_D^{20} 1.4557, d_4^{20} 0.8252.

Found %: C 55.40, 55.67; H 11.42, 11.50. $\text{C}_6\text{H}_{15}\text{BS}$. Calculated %: C 55.40; H 11.62.

n-Butyl ester of diethylthioboric acid. A mixture of 10 g of the ethyl ester of diethylthioboric acid and 10 ml of n-butyl mercaptan, placed in a Favorskii flask, was heated to boiling for 2 hours. In this process the ethyl mercaptan formed and part of the n-butyl mercaptan taken for the reaction were distilled off. Four and six tenths grams (97%) of ethyl mercaptan was obtained. The residue was fractionally distilled. Ten and five tenths grams (86.7%) of the n-butyl ester of diethylthioboric acid was obtained with b.p. 78.5-79.5° at 14 mm, n_D^{20} 1.4603, d_4^{20} 0.8300.

Found %: C 61.06, 61.09; H 12.13, 11.88. $\text{C}_8\text{H}_{19}\text{BS}$. Calculated %: C 60.77; H 12.11.

n-Propyl ester of di-n-propylthioboric acid. To 0.143 mole of tri-n-propylboron was added dropwise 0.154 mole of n-propyl mercaptan at such a rate that the temperature of the reaction mixture did not rise above 60°, which required 15 minutes. Then the reaction mixture was gradually heated to 160° and held at this temperature until the evolution of gaseous products ceased. The experiment lasted about an hour. Three and twenty-five hundredths liters of gas was given off, which contained 0.133 mole of propane, 0.00424 mole of propene, and 0.00424 mole of hydrogen. After fractionation of the liquid products, we obtained 17.96 g (72.5%) of n-propyl ester of di-n-propylthioboric acid with b.p. 93-95° at 15 mm, n_D^{20} 1.4582. This ester had been prepared by us previously from tri-n-propylboron and sulfur and had b.p. of 77.5-78.5° at 7 mm, n_D^{20} 1.4546 [4].

Ethyl ester of di-n-propylthioboric acid. Ninety-five thousandths mole of ethyl mercaptan was added to 0.08 mole of tri-n-propylboron. The temperature of the reaction mixture rose spontaneously to 70°. Then the mixture was heated for 10 minutes at 110°. Seventy-eight thousandths mole of propane was evolved. From the liquid reaction products we obtained 11.4 g (88.5%) of the ethyl ester of di-n-propylthioboric acid with b.p. 99-102° at 46 mm. After repeated distillation the material had b.p. of 72-73° at 13 mm, n_D^{20} 1.4562, d_4^{20} 0.8214.

Found %: C 61.96, 62.03; H 12.40, 12.35. $\text{C}_8\text{H}_{19}\text{BS}$. Calculated %: C 60.77; H 12.11.

All of the esters of dialkylthioboric acids prepared were colorless liquids with an unpleasant odor of mercaptans; they were soluble in organic solvents, easily hydrolyzed and oxidized in the air.

Phenyl ester of di-n-butylthioboric acid. To 0.05 mole of tri-n-butylboron cooled to 0° was added 0.052 mole of thiophenol. The reaction mixture spontaneously heated up. Slow evolution of gas started at about 50°. The mixture was heated for 1.5 hours, with the temperature being gradually raised from 50 to 180°. Twelve hundred and fifty milliliters of gas was given off, containing 0.039 mole of butane, 0.0067 mole of butene, and 0.0081 mole of hydrogen. When the liquid products of the reaction were fractionated, we obtained 10 g (83.1%) of the phenyl ester of di-n-butylthioboric acid, b.p. 140.5-141° at 8 mm, n_D^{20} 1.5136, d_4^{20} 0.9126.

Mobile, colorless liquid, having an unpleasant odor. Soluble in organic solvents, easily oxidized and hydrolyzed.

Found %: C 71.83, 72.05; H 10.06, 10.11; B 4.76. $\text{C}_{14}\text{H}_{23}\text{BS}$. Calculated %: C 71.79; H 9.90; B 4.62.

* All operations were carried out in an atmosphere of nitrogen.

Phenyl ester of di-n-propylthioboric acid. A mixture of 0.12 mole of tri-n-propylboron and 0.126 mole of thiophenol was heated on a metal bath. Weak evolution of gases started at about 85°. Gradually over the course of 2 hours the temperature of the reaction mixture was raised from 100 to 180°. The gas given off (3.2 liters) contained 0.0732 mole of propane, 0.028 mole of propene, and 0.033 mole of hydrogen. After fractionation of the liquid reaction products we obtained 19.5 g (80.2%) of the phenyl ester of di-n-propylthioboric acid with b.p. 130-133° at 15 mm [1].

Action of n-butyl alcohol on n-butyl ester of di-n-propylthioboric acid. In a two-necked flask fitted with a reflux condenser and dropping funnel and connected through the condenser with a gasometer was placed 13.2 g of the n-butyl ester of di-n-propylthioboric acid. Thirteen milliliters of n-butyl alcohol was added, whereupon strong heating of the reaction mixture was observed. The mixture was heated to boiling for 1 hour. The evolution of gaseous products was not observed. The contents of the flask were transferred to a Favorskii flask and fractionated, first at atmospheric pressure and then in vacuum. We obtained 7.4 ml (99%) of n-butyl mercaptan with b.p. 97-98°, 6.5 ml of n-butyl alcohol, and 10.32 g of the n-butyl ester of di-n-propylboric acid, b.p. 76.5-77° at 14 mm, n_D^{20} 1.4139. Literature data: b.p. 76-76.5° at 15 mm, n_D^{20} 1.4133 [9].

Methyl ester of di-n-propylboric acid. In a three-necked flask were placed 0.096 mole of tri-n-propylboron and 0.11 mole of methyl alcohol, and 1 ml of n-butyl mercaptan was added. The mixture spontaneously warmed up to 40°. The reaction mixture was boiled for 6 hours (65-70°). Eighteen hundred and eighty milliliters of gas was given off, containing 0.07 mole of propane. The liquid reaction products were fractionated in vacuum. We obtained 9.45 g (77.5%) of the methyl ester of di-n-propylboric acid with b.p. 54-56° at 44 mm, n_D^{20} 1.4028. The compound had been prepared previously and had b.p. of 55-56° at 44 mm, n_D^{20} 1.4023.

n-Butyl ester of di-n-butylboric acid. To a solution of 13.4 g of tri-n-butylboron in 8 ml of n-butyl alcohol was added 1.5 ml of n-butyl mercaptan. After addition of the mercaptan, the reaction mass spontaneously warmed up to 60°, and the formation of gaseous materials was observed. In the course of 30 minutes the temperature of the mixture was gradually raised to 125°. Twelve hundred milliliters of gas was evolved, the amount of which did not change on further heating at 125°. The gaseous reaction products contained 0.056 mole of butane. After fractionation of the reaction mixture first at atmospheric pressure and then in vacuum, we obtained 13.2 g (90.6%) of the butyl ester of di-n-butylboric acid with b.p. 102-105° at 14 mm, n_D^{20} 1.4212. Literature data: b.p. 92-94° at 8 mm, n_D^{20} 1.4222 [1, 6].

SUMMARY

1. The reaction of trialkyl borons with mercaptans, which leads to the preparation in high yields of the esters of dialkylthioboric acids, has been investigated.
2. A mechanism has been proposed for the reactions of trialkyl borons with compounds containing active hydrogen.
3. It has been shown that the esters of the dialkylthioboric acids react readily with alcohols with the formation of esters of dialkylboric acids.
4. With the higher mercaptans the esters of the dialkylthioboric acids enter into a transesterification reaction ("transmercaptanization").
5. The possibility of preparing esters of dialkylboric acids from trialkyl borons and alcohols, utilizing mercaptans as catalysts, has been shown.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

POLYENE COMPOUNDS

XIV*. SYNTHESIS OF MONOARYLATED POLYENE HYDROCARBONS

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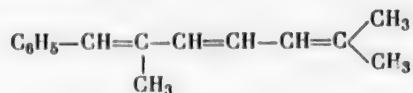
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 1, pp. 167-170,

January, 1961

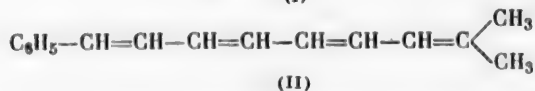
Original article submitted March 27, 1960

The polyene hydrocarbons which have been known up to the present time to have luminescent properties and which have been used as organic luminophors are di- and polyaryl compounds. Aliphatic polyene chains in them are stabilized by terminal aryl radicals which make the hydrocarbon radical comparatively stable in spite of the presence of a large number of double bonds. Thus, 1,10-diphenyl-1,3,5,7,9-decapentaene and higher diphenylpolyenes are quite stable. Monoaryl polyenes in which one end of the polyene chain is not substituted are extremely reactive. For example, 1-phenyl-1,3,5-hexatriene is easily oxidized by oxygen of the air, is cyclized, and undergoes polymerization reactions [1, 2]. Besides the stabilizing action, terminal aryl groups lengthen the total polyene chain of the molecule, giving a greater possibility of electron transfer, which is shown in the luminescent properties of the substances. Thus, 1,6-diphenyl-1,3,5-hexatriene is one of the strongest organic luminophors, while 1-phenyl-1,3,5-hexatriene does not have luminescent properties.

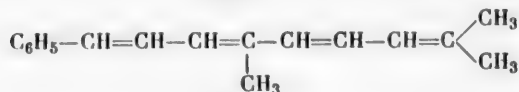
In the present work we have obtained for the first time monoarylated polyene hydrocarbons which have luminescent properties: 2,6-dimethyl-1-phenyl-1,3,5-heptatriene (I), 8-methyl-1-phenyl-1,3,5,7-nonatetraene (II), and 4,8-dimethyl-1-phenyl-1,3,5,7-nonatetraene (III).



(I)



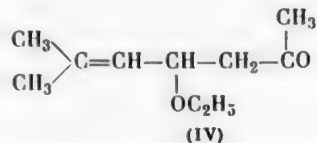
(II)



(III)

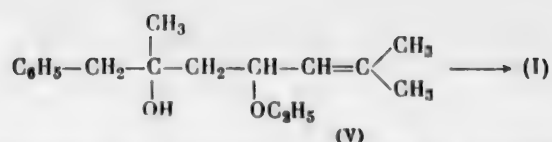
The synthesis of these monoarylated polyene hydrocarbons was carried out by one of the variants worked out for our earlier method [3] using the condensation products of methylcrotonaldehyde acetal with isopropenylethyl ether and ethoxydienes [4, 5].

From the ketal of 4-ethoxy-6-methyl-5-hepten-2-one [4] by hydrolysis we obtained 4-ethoxy-6-methyl-5-hepten-2-one (IV).



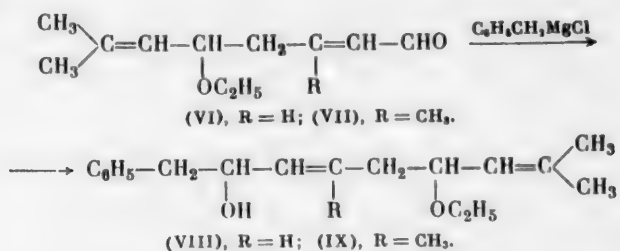
(IV)

*Communication XIII, see *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* 1960, 938.



The ketone (IV) had a characteristic odor and might be of interest as a perfume. When it was condensed with benzylmagnesium chloride it gave 4-ethoxy-2,6-dimethyl-1-phenyl-5-hepten-2-ol (V), which by boiling with an aqueous alcoholic solution of hydrogen bromide was converted to 2,6-dimethyl-1-phenyl-1,3,5-heptatriene (I).

Analogously, from the acetals of 5-ethoxy-7-methyl-2,6-octadien-1-al and 5-ethoxy-3,7-dimethyl-2,6-octadien-1-al [5] were synthesized the corresponding aldehydes (VI) and (VII). By condensation with benzylmagnesium chloride we isolated the corresponding 6-ethoxy-8-methyl-1-phenyl-3,7-nonadien-2-ol (VIII) and 6-ethoxy-4,8-dimethyl-1-phenyl-3,7-nonadien-2-ol (IX), which by removal of the elements of water and alcohol were converted into hydrocarbons (II) and (III).



In the crystalline state 2,6-dimethyl-1-phenyl-1,3,5-heptatriene (I) luminesces weakly in the ultraviolet with a pale violet color, and in solution the luminescence is absent. Polyenes (II) and (III) have a bright blue fluorescence (the latter more intense) in solution and do not luminesce in the solid form.

The methyl group on one of the ends of the polyene aliphatic chain does not have such a stabilizing action as does the phenyl, so that these monoarylated hydrocarbons (I-III) are unstable substances, easily oxidized by oxygen of the air. When heated in solution, they are converted into oily products which makes their purification by recrystallization difficult.

EXPERIMENTAL

4-Ethoxy-6-methyl-5-hepten-2-one (IV). To 5 g of diethylketal of 4-ethoxy-6-methyl-5-hepten-2-one was added 1 ml of 1% H₃PO₄ and 2.5 ml of alcohol. The mixture was shaken for 10 minutes, and when the solution became homogeneous it was allowed to stand for 1.5 hours. The mixture was diluted with ether, neutralized with 4% NaHCO₃ solution, washed with water, and dried over MgSO₄. After distillation of the ether, we obtained 3 g (86%) of 4-ethoxy-6-methyl-5-hepten-2-one.

B.p. 44° (2 mm), d_{20}^{20} 0.8941, n_D^{20} 1.4405, MR 50.23; calc. 49.57.

Found %: C 70.40, 70.64; H 10.47, 10.57. C₁₀H₁₈O₂. Calculated %: C 70.55; H 10.66.

4-Ethoxy-2,6-dimethyl-1-phenyl-5-hepten-2-ol (V). To 0.1 mole of benzylmagnesium chloride in 50 ml of ether was added 0.017 mole of 4-ethoxy-6-methyl-5-hepten-2-one in 20 ml of ether. The mixture was heated with stirring under reflux for five hours, after which it was poured onto ice acidified with 5% hydrochloric acid. The ether layer was neutralized with 4% NaHCO₃, washed with water, and dried over MgSO₄. After distillation of the ether we obtained 2.5 g (54%) of 4-ethoxy-2,6-dimethyl-1-phenyl-5-hepten-2-ol.

B.p. 130-132° (2 mm), d_{20}^{20} 0.9613, n_D^{20} 1.5032, MR 80.70; calc. 80.49.

Found %: C 77.34, 77.54; H 9.77, 9.79. C₁₇H₂₆O₂. Calculated %: C 77.81; H 9.99.

6-Ethoxy-8-methyl-1-phenyl-3,7-nonadien-2-ol (VIII). To 0.5 mole benzylmagnesium chloride in 30 ml of ether was added 0.010 mole of 5-ethoxy-7-methyl-2,6-octadien-1-al dissolved in 15 ml of ether; the aldehyde was obtained by hydrolysis of its diethylacetal [5] with 1% H₃PO₄ and had a b.p. of 66-68° (2 mm), n_D^{20} 1.4705. The reaction occurred in the same way as for compound (V). We obtained 2 g (66.4%) of 6-ethoxy-8-methyl-1-phenyl-3,7-nonadien-2-ol.

B.p. 145-147° (2.5 mm), d_4^{20} 0.9898, n_D^{20} 1.5178, MR 83.98; calc. 83.96.

Found %: C 78.90, 79.15; H 9.42, 9.34. $C_{18}H_{26}O_2$. Calculated %: C 78.79; H 9.55.

6-Ethoxy-4,8-dimethyl-1-phenyl-3,7-nonadien-2-ol (IX). To 0.1 mole of benzylmagnesium chloride in 50 ml of ether was added 0.015 mole of a solution of 5-ethoxy-3,7-dimethyl-2,6-octadien-1-al in 20 ml of ether; the aldehyde was obtained by hydrolysis of its diethylacetal [5, 6]. The reaction was carried out like the preceding one. We obtained 3.5 g (79.4%) of 6-ethoxy-4,8-dimethyl-1-phenyl-3,7-nonadien-2-ol.

B.p. 147-148° (2 mm), d_4^{20} 0.9775, n_D^{20} 1.5120, MR 88.54; calc. 88.57.

Found %: C 79.50, 79.33; H 9.59, 9.59. $C_{19}H_{28}O_2$. Calculated %: C 79.12; H 9.79.

2,6-Dimethyl-1-phenyl-1,3,5-heptatriene (I). To a solution of 0.5 g of 4-ethoxy-2,6-dimethyl-1-phenyl-5-hepten-2-ol in 15 ml of alcohol was added 4 ml of concentrated hydrobromic acid. The mixture was boiled in a stream of nitrogen under reflux for 10 minutes and left overnight in the refrigerator. The crystals which precipitated were filtered off, washed on the filter with a small amount of alcohol, then with water, and dried in a vacuum. We obtained 0.2 g of 2,6-dimethyl-1-phenyl-1,3,5-heptatriene in the form of pale yellow crystals with m.p. 60-61°. After careful dilution of the filtrate with water there precipitated on standing for a day another 0.1 g of crystals. Total yield 79%.

Found %: C 90.42, 90.42; H 9.00, 9.22. $C_{15}H_{18}$. Calculated %: C 90.85; H 9.15.

8-Methyl-1-phenyl-1,3,5,7-nonatetraene (II). To a solution of 0.5 g of 6-ethoxy-8-methyl-1-phenyl-3,7-nonadien-2-ol in 15 ml of alcohol was added 4 ml of concentrated hydrobromic acid. The reaction was carried out as above in preparing 2,6-dimethyl-1-phenyl-1,3,5-heptatriene. After recrystallization from alcohol we obtained 0.26 g of 8-methyl-1-phenyl-1,3,5,7-nonatetraene in the form of light yellow crystals with m.p. 80-83°.

Found %: C 91.21, 91.04; H 8.54, 8.45. $C_{16}H_{18}$. Calculated %: C 91.37; H 8.63.

4,8-Dimethyl-1-phenyl-1,3,5,7-nonatetraene (III). To a solution of 1 g of 6-ethoxy-4,8-dimethyl-1-phenyl-3,7-nonadien-2-ol in 30 ml of alcohol was added 8 ml of concentrated hydrobromic acid. The reaction was carried out as described above. We obtained 0.37 g (47.6%) of substance in the form of light yellow crystals with m.p. 112-113° (from alcohol).

Found %: C 91.25, 90.53; H 9.00, 8.93. $C_{17}H_{20}$. Calculated %: C 91.01; H 8.99.

SUMMARY

By condensation of benzylmagnesium chloride with 4-ethoxy-6-methyl-5-hepten-2-one, 5-ethoxy-7-methyl-2,6-octadien-1-al, and 5-ethoxy-3,7-dimethyl-2,6-octadien-1-al we obtained the corresponding 4-ethoxy-2,6-dimethyl-1-phenyl-5-hepten-2-ol, 6-ethoxy-8-methyl-1-phenyl-3,7-nonadien-2-ol, and 6-ethoxy-4,8-dimethyl-1-phenyl-3,7-nonadien-2-ol.

By boiling these ethoxy alcohols with hydrobromic acid we formed the monoaryl polyene hydrocarbons with luminescent properties: 2,6-dimethyl-1-phenyl-1,3,5-heptatriene, 8-methyl-1-phenyl-1,3,5,7-nonatetraene, and 4,8-dimethyl-1-phenyl-1,3,5,7-nonatetraene.

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STUDIES IN THE FIELD OF DERIVATIVES OF β -DICARBOXYL COMPOUNDS

III. THE SYNTHESIS OF 4-SUBSTITUTED PYRAZOLES

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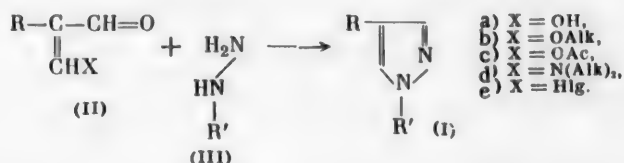
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Homologs of pyrazole which contain substituents in positions 3 and 5 of the pyrazole ring are easily obtained by condensation of β -ketoaldehydes [1], β -diketones [2], or functional derivatives of these compounds [3] with hydrazine or substituted hydrazines. The 4-substituted pyrazoles are much less available; the syntheses of individual examples of compounds of this type (I, $R = CH_3$ [4-7]; $R = C_2H_5$ [8]; $R = C_6H_5$ [9-13]) have been carried out by various methods, some rather complicated. It was shown recently that unsubstituted pyrazole and *N*-arylpyrazoles can be obtained through the tetraacetal of malondialdehyde or other functional derivatives of this [14-17]. In view of the fact that at the present time full acetals of homologs of malondialdehyde have also become available [18], we have investigated the possibility of using these compounds as starting substances for the synthesis of 4- and 1,4-substituted pyrazoles [19].

Contrary to the β -ketoacetals [20] the full acetals of homologs of malondialdehydes do not react with hydrazine or with arylhydrazines, either directly or in the presence of alkaline catalysts. However, the formation of pyrazoles takes place in the case of preliminary hydrolysis of the acetals by heating with aqueous solutions of acids, where the evolution of the dialdehyde (II a) is not necessary (process A), or as a result of reaction of the acetals with an aqueous solution of salts of hydrazine or arylhydrazines (acid catalyst; process B); typical examples are given in the experimental part. 4-Substituted pyrazoles are also formed smoothly if instead of the acetal of substituted malondialdehydes we use functional derivatives of the enol form of the dialdehyde (cf. [21]), that is, β -alkoxyacroleins (II b, process C), β -acyloxyacroleins (II c, Process D), or β -dialkylaminoacroleins (II d, Process E); we have reported earlier on the use for this purpose of one or another β -haloacrolein (IIe) [17].

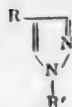


Probably in all the processes considered above for obtaining pyrazoles, there are obtained as intermediate reaction products the corresponding nitrogen derivatives of the aldehydes (II) on the carbonyl group; in favor of this is the possibility of obtaining the isolated arylhydrazones of β -haloacroleins [17] and semicarbazones of β -acyloxyacroleins [16] which are easily cyclized by the action of acids into pyrazoles, and also the conversion of di-*p*-nitrophenylhydrazones of ethylmalondialdehyde, obtained under other conditions, into 1-*p*-nitrophenyl-4-ethylpyrazole.

In the reaction of the acetals of alkylmalondialdehydes with salts of semicarbazide (III, $R' = CONH_2$) we isolated the crystalline amide of 4-alkylpyrazole-1-carboxylic acid (I, $R' = CONH_2$), which by treatment with acids was hydrolyzed and decarboxylated to form pyrazoles (I, $R' = H$).

4-Alkylpyrazoles are stable liquids which distill without decomposition and are soluble in organic solvents; they were characterized as picrates (1-aryl-4-alkylpyrazoles, as the chloroplatinates). For the calculation of molecular refraction of substituted pyrazoles, see [3]; in the case of 1-arylpyrazoles as the increment for both nitrogens we used the value 3.46.

4-Substituted Pyrazoles



R	R'	Method of preparation	Yield, %	B.p. (m.p.) ^a	Empirical formula
CH ₃	H	{ A B	66.9 73.1	70–73° (3 mm) 98–100 (6 mm) [7]	{ C ₄ H ₆ N ₂
C ₂ H ₅	H	{ A C D	57.2 52.0 68.4	82–85 (3mm) ^b	C ₅ H ₈ N ₂
iso-C ₃ H ₇	H	A	54.4	90–91 (3mm) ^c	C ₆ H ₁₀ N ₂
C ₆ H ₅	H	{ A E	62.5 69.2	M.p. 230–231 M.p. 230 [13]	{ C ₆ H ₈ N ₂
CH ₃	C ₆ H ₅	A	79.1	98–100 (1.5 mm) M.p. 42–43 [11] M.p. 42–43	{ C ₁₀ H ₁₀ N ₂
C ₂ H ₅	C ₆ H ₅	{ A B	74.1 68.6	114–115 (2 mm) ^d	C ₁₁ H ₁₂ N ₂
iso-C ₃ H ₇	C ₆ H ₅	A	75.2	118–120 (1.5 mm) ^e	C ₁₂ H ₁₄ N ₂
C ₆ H ₅	C ₆ H ₅	A	77.8	M.p. 98–99 M.p. 97 [12]	{ C ₁₅ H ₁₂ N ₂
CH ₃	p-O ₂ NC ₆ H ₄	A	60.5	M.p. 123–124 M.p. 120 [6]	{ C ₁₀ H ₈ O ₂ N ₂
C ₂ H ₅	p-O ₂ NC ₆ H ₄	A	80.4	M.p. 74–75	C ₁₁ H ₁₁ O ₂ N ₂
iso-C ₃ H ₇	p-O ₂ NC ₆ H ₄	A	56.2	M.p. 101–102	C ₁₂ H ₁₃ O ₂ N ₂

^aFor some substances we give literature data at the end.

^b n_D^{20} 1.4907, d_4^{20} 0.9862, MR_D 28.21; calc. 28.40. Found %: C 62.95; H 8.69. Calculated %:

C 62.47; H 8.86.

^c n_D^{20} 1.4830, d_4^{20} 0.9706, MR_D 32.41; calc. 33.02.

^d n_D^{20} 1.5791, d_4^{20} 1.0657, MR_D 53.71; calc. 53.64.

^e n_D^{20} 1.5630, d_4^{20} 1.0390, MR_D 58.21; calc. 58.26.

We recently showed that the tetraacetal of malondialdehyde can easily be converted into chloro- or bromo-malondialdehyde or acetals of these compounds [22], which opens the possibility of a simple synthesis of 4-chloro- or 4-bromopyrazole. This reactions requires more severe conditions than in the case of obtaining 4-alkylpyrazoles; probably cyclization of the intermediate hydrazone or arylhydrazones of halomalondialdehydes (which could not be isolated in the individual state) occurs only with heating with a sufficiently concentrated acid solution.

EXPERIMENTAL*

Obtaining 4-Substituted Pyrazoles

Process A. From acetals of homologs of malondialdehyde. 4-Methylpyrazole. A mixture of 4.68 g of 1,1,3,3-tetraethoxy-2-methylpropane and 5 ml of 0.5 N solution of hydrochloric acid were mixed for 1 hour at 50°. To the resulting homogeneous solution was added a solution of 1.4 g of hydrazine hydrochloride in 2 ml of water, and the mixture was heated for two hours at 60°, cooled, made alkaline with potassium hydroxide to pH 9, saturated with

*The melting and boiling points given in text and table are uncorrected.

% N		M.p. of derivative ^a (solvent for crystallization)	Empirical formula	Found (%)		Calculated (%)	
found	calc.			N	H ₂ O	N	H ₂ O
25.15, 25.21	25.43	Picrate, 140-141°, 139.5° [7]	C ₁₀ H ₉ O ₇ N ₅	—	—	—	—
		Picrate, 144-145° (from water)	C ₁₁ H ₁₁ O ₇ N ₅	21.89, 21.84	—	21.53	—
		Picrate, 114-116° (from alcohol)	C ₁₂ H ₁₃ O ₇ N ₅	20.61, 20.69	—	20.65	—
		Picrate, 154-155°, 155° [13]	C ₁₃ H ₁₁ O ₇ N ₅	—	—	—	—
16.55, 16.51	16.28	Chloroplatinate 110-112.5° (from aqueous HCl)	2C ₁₁ H ₁₃ N ₂ · H ₂ PtCl ₆ · 2H ₂ O	7.16, 7.22	4.25	7.09	4.55
14.82, 14.77	15.04	Chloroplatinate, 109-111.5° (from aqueous HCl)	2C ₁₂ H ₁₄ N ₂ · H ₂ PtCl ₆ · 2H ₂ O	6.75, 6.96	4.52	6.96	4.47
13.03, 13.07	12.73	Chloroplatinate, 180-181° (from aqueous HCl)	2C ₁₃ H ₁₅ N ₂ · H ₂ PtCl ₆ · 2H ₂ O	5.84, 6.11	3.60	6.33	4.06
19.36, 19.54	19.30						
18.41, 18.45	18.17						

sodium chloride, and repeatedly extracted with ether. The ether extract was dried over K₂CO₃. After distillation of the solvent and redistillation we obtained 1.1 g (66.9%) of 4-methylpyrazole (see table).

In obtaining 1-phenyl- and 1-p-nitrophenyl-substituted pyrazoles the reaction mixture was heated four hours at 70°. The water-insoluble p-nitrophenylhydrazine was brought into reaction in the form of an acidified alcohol solution.

Process B. Acid catalyst. 1-Phenyl-4-ethylpyrazole. A mixture of 4.96 g of 1,1,3,3-tetraethoxy-2-ethylpropane, 2.8 g of phenylhydrazine hydrochloride, and 10 ml of water was stirred for two hours at 70-80°. After cooling the reaction mixture it was made alkaline with potassium hydroxide and extracted with ether. The residue after evaporation of the ether was vacuum distilled. We obtained 2.36 g (68.6%) of 1-phenyl-4-ethylpyrazole.

Process C. From β-alkoxyacroleins. 4-Ethylpyrazole. To a solution of 0.7 g of hydrazine hydrochloride in 3 ml of water was added dropwise 1.14 g of α-ethyl-β-methoxyacrolein [23]; the mixture was stirred for two hours at 50°, cooled, made alkaline with potassium hydroxide to pH 9, saturated with sodium chloride, and extracted with ether. After evaporation of the ether and distillation, we obtained 0.5 g (52%) of 4-ethylpyrazole.

Process D. From β -acyloxyacroleins. 4-Ethylpyrazole. To a solution of 0.2 g of hydrazine hydrate in 2 ml of methanol was added 0.56 g of α -ethyl- β -acetoxyacrolein (cf. [16]); after 15 minutes the mixture was made alkaline with potassium hydroxide and extracted with ether. After removal of the ether and distillation we obtained 0.26 g (68.4%) of 4-ethylpyrazole.

Under analogous conditions from 0.4 g of methyl- β -(α -ethyl)-acrolein carbonate (cf. [16]) and 0.15 g of hydrazine hydrate we obtained 0.14 g (58.3%) of 4-ethylpyrazole.

Process E. From β -dialkylaminoacroleins. 4-Phenylpyrazole. A solution of 0.2 g of hydrazine hydrate in 6 ml of methanol was mixed with 0.4 g of α -phenyl- β -diethylaminoacrolein [24]; a precipitate of crystals began to come down rather slowly. For completion of the reaction, the mixture was heated for five minutes on a boiling water bath. After cooling, 0.2 g (69.2%) of 4-phenylpyrazole precipitated.

Di-p-nitrophenylhydrazone of ethylmalondialdehyde. To a solution of 1.5 g of p-nitrophenylhydrazine in 25 ml of alcohol was added 0.6 g of sodium ethylmalondialdehyde and several drops of acetic acid. After three hours the precipitate was filtered off and washed with alcohol. We obtained 1.15 g (62.1%) of orange crystals, m.p. 203-206°.

Found %: N 23.08. $C_{17}H_{18}O_4N_6$. Calculated %: N 22.80.

A mixture of 0.23 g of dihydrazone, 1 ml of 0.1 N hydrochloric acid, and 1 ml of alcohol was heated for three hours on a water bath; the hot solution was filtered through charcoal. When it cooled, 0.1 g (76.9%) of 1-p-nitrophenyl-4-ethylpyrazole precipitated.

Amide of 4-methylpyrazole-1-carboxylic acid. To a solution of 1.16 g of semicarbazide hydrochloride in 4 ml of water was added with stirring 2.34 g of 1,1,3,3-tetraethoxy-2-methylpropane. The mixture was stirred for 2.5 hours at room temperature; the crystals which precipitated were filtered off and washed with hot alcohol and ether. M.p. 137.5-139° (from aqueous alcohol). Yield 1.05 g (83.9%).

Found %: N 33.96, 33.72. $C_8H_7ON_3$. Calculated %: N 33.56.

We obtained the following compounds in an analogous way.

Amide of 4-ethylpyrazole-1-carboxylic acid (yield 78.3%), m.p. 105-105.5° (from aqueous alcohol).

Found %: N 30.42, 30.49. $C_8H_9ON_3$. Calculated %: N 30.19.

Amide of 4-isopropylpyrazole-1-carboxylic acid (yield 52.3%), m.p. 104-104.5° (from aqueous alcohol).

Found %: C 54.63, 54.61; H 7.24, 7.39. $C_7H_{11}ON_3$. Calculated %: C 54.92; H 7.23.

A mixture of 2.2 g of the amide of 4-methylpyrazole-1-carboxylic acid and 30 ml of 10% hydrochloric acid solution was heated for two hours on a boiling water bath. The cooled reaction mixture was made alkaline with a solution of potassium hydroxide, saturated with sodium chloride, and extracted with ether; the residue after evaporation of the ether was distilled in a vacuum. We obtained 1.2 g (83.3%) of 4-methylpyrazole, b.p. 71-75° (3 mm).

Picrate, m.p. 140-141°.

In an analogous way we obtained 4-ethyl- and 4-isopropylpyrazoles from the corresponding amides of the 4-alkylpyrazole-1-carboxylic acids.

4-Bromopyrazole. A mixture of 3.02 g of bromomalondialdehyde, 1.7 g of hydrazine hydrochloride, and 10 ml of a water solution of hydrochloric acid (1:1) was heated to boiling for ten minutes and after cooling was made alkaline with a concentrated solution of sodium hydroxide and was extracted with ether. The crystalline residue after evaporation of the ether was dried in a vacuum over phosphoric anhydride at 30-40°; yield 1.9 g (64%); after recrystallization from water, m.p. 93-94°; according to the literature [25], m.p. 95-97°.

In an analogous way we obtained from chloromalondialdehyde 4-chloropyrazole, m.p. 71-73° (yield 60%); after crystallization from water, m.p. 76-77°; according to the literature [25], m.p. 69-71°.

1-Phenyl-4-chloropyrazole. A mixture of 3.2 g of chloromalondialdehyde, 15 ml of acetic acid, 5 ml of concentrated hydrochloric acid, and 4.3 g of phenylhydrazine hydrochloride was heated to boiling for 15 minutes, treated with charcoal, and the filtrate then poured into 300 ml of water. The crystals which precipitated were filtered off; weight 4.1 g (77%), m.p. 71-73°; after recrystallization from aqueous alcohol and vacuum drying,

1-phenyl-4-chloropyrazole had m.p. of 74-75°; according to the literature [26], m.p. 75°.

1-Phenyl-4-bromopyrazole. A mixture of 2.9 g of 1,1,3,3-tetraethoxy-2-bromopropane and 5 ml of a water solution of hydrochloric acid (1:1) was heated on a water bath to disappearance of the acetal layer. To the resulting solution was added 1.5 g of phenylhydrazine hydrochloride in 15 ml of water; the mixture was heated for two hours to boiling and was steam distilled; we obtained 1.25 g (56%) of 1-phenyl-4-bromopyrazole with m.p. 77-78°. After recrystallization from aqueous alcohol, m.p. 78-79°; according to the literature [27] m.p. 81°.

1-p-Nitrophenyl-4-chloropyrazole. To 1.06 g of chloromalondialdehyde dissolved in a mixture of 25 ml of alcohol and 20 ml of concentrated hydrochloric acid we added 1.5 g of p-nitrophenyl hydrazine. The mixture was heated for 20 minutes at boiling, after which it was poured into 100 ml of water; the precipitate was filtered off and recrystallized from 90% alcohol and dried in a vacuum at 40°. Yield 1.4 g (64%), m.p. 145.5-146.5°.

Found %: N 18.70; Cl 15.52. $C_9H_6O_2N_2Cl$. Calculated %: N 18.83; Cl 15.85.

In an analogous way we obtained 1-p-nitrophenyl-4-bromopyrazole (68%), m.p. 168-169° (from alcohol).

Found %: Br 30.39, 30.32; N 15.90, 16.00. $C_9H_6O_2N_2Br$. Calculated %: Br 29.81; N 15.67.

SUMMARY

By the reaction of acetals of homologs of malondialdehyde or their functional derivatives with hydrazine or arylhydrazines we have a suitable method for obtaining 4- or 1,4-substituted pyrazoles.

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REACTIONS OF ACID PHOSPHITES, THIOPHOSPHITES, PHOSPHONITES, AND DIALKYLPHOSPHINE OXIDES WITH DISULFIDES

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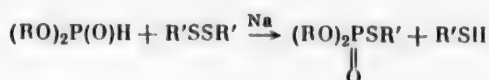
Original article submitted February 2, 1960

We showed previously that sodium dialkylphosphites react with disulfides with formation of thiolophosphates and mercaptides [1]:



These reactions could be used under laboratory conditions for the synthesis of various thiolophosphates. However, in preparing larger quantities of thiolophosphates, because of the necessity for using equimolecular amounts of sodium, this method is uneconomic and is comparatively difficult to carry out.

In the present work we have continued our study of these reactions and shown that disulfides react with acid phosphites, thiophosphites, phosphonites, and dialkylphosphines with formation of the corresponding thiol derivatives in the presence of catalytic amounts of metallic sodium, and in some cases, even in its absence. Thus, in treatment of equimolecular mixtures of acid phosphites and dialkyl disulfides with small amounts (0.1-0.3 mole %) of sodium under conditions which assure rapid distillation of the mercaptan, there is formed in almost quantitative yield the corresponding thiolophosphate.

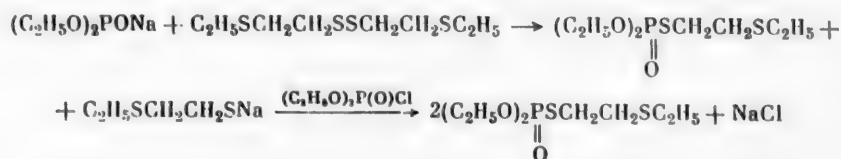


The following is the mechanism of this reaction: Under the influence of the catalytic amount of sodium on the mixture of disulfides and dialkylphosphites the latter form salts which react with the disulfides by the equation given above; the presence in the reaction mass of phosphites and mercaptides leads to establishment of the equilibrium

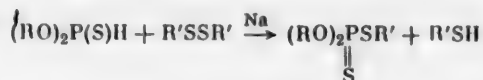


Shift of the equilibrium to the right is produced by distillation of mercaptan from the reaction mass. Reaction takes place more easily when the resulting mercaptan has a low boiling point and is difficult when the boiling points of the phosphite and mercaptan are comparatively close. Thus, under the influence of sodium on the mixture of diethylphosphite and β,β' -diethylthioethyl disulfide we obtain thiolophosphate ("isosystox") contaminated by disulfide. When in the same reaction we use with the disulfide the dibutylphosphite, whose boiling point is considerably higher than the boiling point of ethylthioethyl mercaptan, O,O-dibutyl-S-ethylthioethylphosphate is formed in good yield.

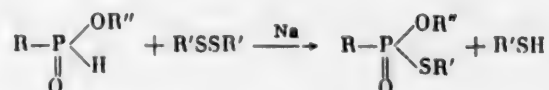
O,O-Diethyl-S-ethylthioethylphosphate ("isosystox") was obtained in good yield by successive treatment of sodium diethylphosphite with diethylthioethyl disulfide and diethylchlorophosphate.



Dialkylthiophosphites under the influence of small addition of sodium also react with disulfides with great ease, forming good yields of dithiophosphates.

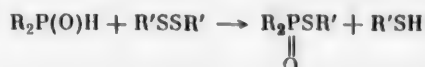


Monoalkylphosphonites, though they have less acid properties than do dialkylphosphites and thiophosphites, which naturally makes difficult the shift in the equilibrium shown above, yet also react smoothly enough with disulfides, forming thiolophosphonates.



In some cases phosphonites react with disulfides with small yields of thiolophosphonates even in the absence of sodium. The occurrence of this reaction can be explained by the fact that phosphonites are stronger reducing agents than are phosphites and thiophosphites.

Dialkylphosphine oxides, which do not have acid properties at all but are strong reducing agents, form good yields of thiolophosphonates with disulfides in the absence of sodium.



Thus, the reaction of disulfides with acid phosphites and phosphonites is determined by the acid and reducing properties of the latter.

EXPERIMENTAL

Thiolophosphates and phosphonates (typical method). To an equimolecular mixture of dialkylphosphite (thiophosphite, monoalkylphosphonite, dialkylphosphine oxide) and dialkyldisulfide, heated to 100-110° in a vacuum distilling flask, was added 0.1-0.3 mole % of sodium*. The mixture was heated at 110-140° in a vacuum in a stream of dry nitrogen. Temperature and evacuation were so regulated that the mercaptan distilled from the reaction mass, and the phosphite (phosphonite) did not distill. When the boiling points of the mercaptan and phosphite (phosphonite) were close to each other, the latter was used in excess. When nearly the calculated amount of mercaptan had been collected in the receiver, the reaction was considered to be ended. Sodium was added repeatedly when the reaction slowed down. The residue after distillation of the mercaptan in most cases was practically pure thiophosphate (phosphonate) which distilled almost completely in a range of 1-3°. The yield of distilled product was 75-95%. The properties of the resulting compounds and analytical data are given in the table.

O,O-Diethyl-S-ethylthioethylphosphate. To 0.1 mole of Na diethylphosphite in 75 ml of anhydrous toluene was added with stirring 0.1 mole of β,β'-diethylthioethylsulfide, upon which warming occurred. After keeping for one hour at 23-30°, 0.1 mole of diethylchlorophosphate was added to the reaction mass. For completion of the reaction the mixture was heated for one hour on a water bath, then after cooling was washed with water. The solvent was distilled from the organic layer in a vacuum and the residue was distilled. We obtained 0.16 mole (80%) of the substance.

B.p. 163-165° (5 mm), d_4^{20} 1.1346, n_D^{20} 1.4995, M_R 66.91. Calc. 66.26. According to the literature [5], b.p. 100-105° (0.025 mm), d_4^{25} 1.1269, n_D^{25} 1.4922.

Found %: S 25.11; P 12.24. $\text{C}_8\text{H}_{19}\text{O}_3\text{S}_2\text{P}$. Calculated %: S 24.82; P 11.99.

β,β'-Diethylthioethylsulfide. We heated 28.8 g of crystalline sodium sulfide in 100 ml of alcohol with stirring until it dissolved. Then in portions we added 3.84 g of powdered sulfur, and heating was continued until it dissolved. To the resulting solution of sodium disulfide we added 30 g of β-chloroethylsulfide. The reaction mass was boiled for eight hours. The sodium chloride was filtered off; the solvent was distilled from the filtrate; the

*In the case of the dialkylphosphine oxides, the sodium was not added.

Thioliophosphates, Dithiophosphates, and Thioliophosphonates

No.	Formula	B.p. (pressure in mm)	d_4^{20}	n_D^{20}	M_R^*		Found, %		Empirical formula	Calculated, %	
					found	calc.	P	S		P	S
1	$(C_6H_5O)_2P(O)SC_4H_9$	103—105° (6)	1.1082	1.4583	48.83	48.95	15.31	16.15	$C_6H_{13}O_3SP$	15.63	16.18
2	$(n-C_4H_9O)_2P(O)SC_4H_9$	127—128 (8)	1.0516	1.4364	58.54	58.37	13.38	14.40	$C_8H_{19}O_3SP$	13.69	14.17
3	$(iso-C_4H_9O)_2P(O)SC_4H_9$	113—116 (12)	1.0452	1.4303	58.21	58.41	13.18	14.33	$C_8H_{19}O_3SP$	13.69	14.17
4	$(n-C_4H_9O)_2P(O)SC_2H_5$	143—145 (7)	1.0273	1.4587	67.64	67.72	11.90	12.75	$C_6H_{13}O_3SP$	12.18	12.61
5	$(iso-C_4H_9O)_2P(O)SC_2H_5$	131—134 (7)	1.0152	1.4510	67.46	67.80	12.30	12.55	$C_{10}H_{23}O_3SP$	12.18	12.61
6	$(C_6H_5O)_2P(O)SC_4H_9-n$	131—133 (10)	1.0527	1.4596	58.83	58.54	13.48	14.41	$C_8H_{19}O_3SP$	13.69	14.17
7	$(C_6H_5O)_2P(O)SC_2H_5-iso$	129—131 (11)	1.0591	1.4588	58.38	58.41	13.35	14.53	$C_8H_{19}O_3SP$	13.69	14.17
8	$(n-C_4H_9O)_2P(O)SCH_2CH_2SC_4H_9$	193—195 (4.5)	1.0643	1.4952	86.19	85.02	9.77	20.21	$C_{12}H_{27}O_3S_2P$	9.85	20.44
9	$(C_6H_5O)_2P(S)SC_4H_9$	123—124 (11)	1.1109	1.4920	55.96	55.99	14.39	30.15	$C_8H_{15}O_3S_2P$	14.45	29.93
10	$(C_6H_5O)_2P(S)SC_2H_5-n$	124—126 (6)	1.0664	1.4880	65.47	65.37	12.31	26.70	$C_8H_{19}O_3S_2P$	12.78	26.46
11	$(C_6H_5O)_2P(S)SC_4H_9-iso$	117—119 (5)	1.0646	1.4834	65.06	65.41	12.98	26.15	$C_8H_{19}O_3S_2P$	12.78	26.46
12	$(n-C_4H_9O)_2P(S)SC_4H_9$	141—142 (4)	1.0349	1.4840	74.75	74.76	11.50	23.46	$C_{10}H_{23}O_2S_2P$	11.46	23.72
13	$(n-C_4H_9O)_2P(S)SC_2H_5-n$	158 (4)	1.0116	1.4820	84.11	84.15	10.46	20.98	$C_{12}H_{27}O_2S_2P$	10.14	21.49
14	$(n-C_4H_9O)_2P(S)SC_2H_5-iso$	151—152 (5)	1.0044	1.4808	84.53	84.19	10.30	21.63	$C_{12}H_{27}O_2S_2P$	10.14	21.49
15	$CH_3P(O)(OC_6H_5)SC_4H_9$	95—97 (10)	1.0933	1.4730	43.16	43.13	18.10	18.35	$C_8H_{13}O_3SP$	18.47	19.06
16	$CH_3P(O)(OC_6H_5-n)SC_4H_9$	109—110 (12)	1.0612	1.4718	48.07	47.84	16.75	17.13	$C_8H_{13}O_3SP$	17.00	17.60
17	$CH_3P(O)(OC_6H_5-iso)SC_4H_9$	94—95 (9)	1.0518	1.4660	47.98	47.86	16.92	17.41	$C_8H_{13}O_3SP$	17.00	17.60
18	$CH_3P(O)(OC_6H_5-n)SC_2H_5$	115—117 (9)	1.0429	1.4698	52.48	52.52	14.98	16.04	$C_7H_{17}O_3SP$	15.78	16.34
19	$CH_3P(O)(OC_6H_5-iso)SC_2H_5$	111—112 (11)	1.0327	1.4663	52.66	52.56	15.30	16.35	$C_7H_{17}O_3SP$	15.78	16.34
20	$CH_3P(O)(OC_6H_5-iso)SC_4H_9-n$	127—128 (8)	1.0038	1.4664	61.94	61.94	13.58	14.38	$C_9H_{21}O_3SP$	13.81	14.30
21	$(n-C_4H_9)_2P(O)SC_4H_9$	200—202 (3)	—	—	—	—	9.20	9.26	$C_{18}H_{39}OSP$	9.26	9.58
22	$(n-C_4H_9)_2P(O)SC_2H_5-n$	M.p. 37°	0.9148	1.4770	112.0	112.33	8.30	8.70	$C_{20}H_{43}OSP$	8.54	8.84
23	$(n-C_4H_9)_2P(O)SC_2H_5-iso$	234—236 (5) 222—224 (5)	0.9116	1.4777	112.5	112.37	8.36	9.20	$C_{20}H_{43}OSP$	8.54	8.84

* Values for atomic refraction of sulfur are taken: $AR_{-S} = 8.46$ and $AR_S = 9.25$. Literature data: No. 1, b.p. 120° (17 mm), n_D^{20} 1.4560 [2]; No. 4, b.p. 152—153° (12 mm), n_D^{20} 1.4548 [2]; No. 6, b.p. 137° (15 mm), n_D^{20} 1.4580 [2]; No. 9, b.p. 115—115.5° (10 mm), n_D^{20} 1.5013, d_4^{20} 1.1168 [3]; No. 13, b.p. 148—149° (4 mm), n_D^{20} 1.4859, d_4^{20} 1.0159 [3]; No. 15, b.p. 106—108° (18 mm), n_D^{20} 1.4718, d_4^{20} 1.0904 [4]; No. 16, d.p. 71—72° (3 mm), n_D^{20} 1.4510, d_4^{20} 1.0356 [4]; No. 17, b.p. 60—62° (1 mm), n_D^{20} 1.4749, d_4^{20} 1.0555 [4]; No. 19, b.p. 69—70° (1 mm), n_D^{20} 1.4686, d_4^{20} 1.0222 [4].

residue was dissolved in benzene and washed with water. The solvent was distilled from the benzene solution, and the residue was distilled. We obtained 18.9 g (65%) of the substance.

B.p. 159-164° (3.5 mm), d_4^{20} 1.1028, n_D^{20} 1.5675, M_R 71.88. Calc. 71.26. Found %: S 51.91. $C_8H_{10}S_4$. Calculated %: S 52.89.

SUMMARY

We have worked out a process for obtaining thiolophosphates and phosphonates by the reaction of dialkyldisulfides with acid phosphites, thiophosphites, phosphonites, and dialkylphosphine oxides.

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MONOALKOXYMETHYLTHIOPHOSPHONATES AND MONOALKOXYMETHYLPHOSPHONITES

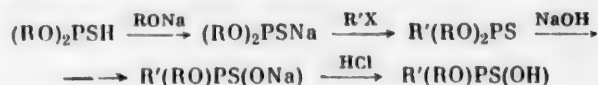
K. A. Petrov, N. K. Bliznyuk, Yu. N. Studnev, and A. F. Kolomiets

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 1, pp. 179-184,

January, 1961

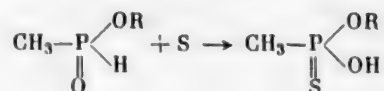
Original article submitted February 2, 1960

Monoesters of alkylthiophosphinic acid have recently interested many investigators [1, 2]; they are used as intermediates in the synthesis of various compounds. Monoalkyl thiophosphonates were first obtained [1] by the scheme



Later this process was somewhat modified [3]. Some monoesters of ethylthiophosphinic acid were obtained by adding sulfur to the potassium monoalkylphosphinites [4].

In the present work we have studied the reaction of addition of sulfur to monoesters of methylphosphinous acid in order to find a simpler way to synthesize the compounds.

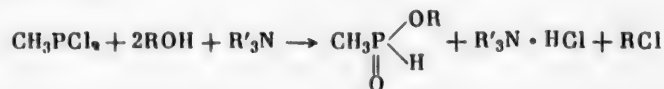


It was shown that the rate of this reaction, as in the case of the dialkylphosphites [5], depends chiefly on the nature of the solvent used. While the reaction takes place smoothly and with sufficient speed in dioxane, in ether under even more severe conditions it scarcely occurs. Like the dialkylphosphites [6], monoalkylphosphonites in ether solution bind sulfur only in the presence of bases such as triethylamine.

The rate of reaction of sulfur with monoalkylphosphonites is greater than with dialkylphosphites, which agrees fully with the change in electron density on the phosphorus atom. By analogy with the dialkylphosphites [7] we can consider that the addition of sulfur to monoalkylphosphonites in proton-acceptor solvents is not connected with a tautomeric change of these compounds into derivatives of trivalent phosphorus.

The structure of the resulting monoalkylthiophosphinic acid was shown by its conversion to a salt and a neutral ester.

The monoesters of methylphosphinous acid, not previously described in the literature, were obtained with yields of 90% by reaction of methyldichlorophosphine with alcohols in the presence of tertiary amines at a mole ratio of reagents of 1 : 2 : 1, respectively.



In selecting the ratios of reagents, the role of hydrogen chloride acceptor is taken not only by the tertiary amine, but also by the neutral phosphonite formed in the reaction [8-10]; this is then converted to the monoester and alkyl chloride.



The earlier described method [11-13] for obtaining monoesters of alkylphosphinous acid from alkylchlorophosphine and alcohols (without a tertiary amine) in a number of cases is unsuitable for the synthesis of derivatives of methylphosphinous acid. This is due to the great tendency of these compounds, especially the lower members of the series, to be dealkylated.



The monoalkoxymethylphosphonites are colorless, almost odorless mobile liquids, easily soluble in organic solvents, and, for the lower members of the series, in water. They are stable on keeping: When carefully protected from access of moisture and air they do not change after standing for a year.

The calculated average values for atomic refraction of phosphorus (AR^{P}) in the monoesters of methylphosphinous acid which we synthesized and the previous [13] acid ethylphosphonites is 5.02° which differs from the value for AR^{P} in dialkylphosphites by 0.52. ** Thus, on going from dialkylphosphites to monoalkylphosphonites there is the same regularity of change of AR^{P} as has been found for the compounds of pentavalent phosphorus. This fact, and also the sharp difference of AR^{P} in mono- and dialkylphosphonites (by 2.72) suggests that phosphorus in monoalkylphosphonites, as in dialkylphosphites [7] and dialkylphosphine oxides [15], occurs in the pentavalent state.

There is an especially sharp change in the value for AR^{P} (by 2.5-3 units) in going from derivatives of pentavalent to derivatives of trivalent phosphorus. This permits a simple determination (by specific gravity and index of refraction) of the valence of phosphorus and indicates the dominant structure of compounds which are capable of tautomeric transformations (dialkylphosphites, monoalkylphosphonites). The value of AR^{P} in derivatives of phosphorus with the same valence changes to a lesser degree (0.5-0.7 units), and this change occurs in full agreement with the electrophilic character of the atoms or radicals bound to the phosphorus.

It should be remarked that in view of the considerable change in value of AR^{P} in going from one class of organic phosphorus compounds to another there is no basis for considering that it will remain constant for a given class. Therefore the value of AR^{P} which is usually used in calculating the molecular refraction must be considered as a very approximate average value. The agreement or disagreement between observed and calculated values of MR for organic phosphorus compounds cannot always be a criterion of their purity.

EXPERIMENTAL

Monoethyl ester of methylthiophosphinic acid. To a solution of 0.1 mole of the monoethyl ester of methylphosphinous acid in 50 ml of anhydrous dioxane was added 0.14 g-atom of powdered sulfur. The reaction mass was heated with stirring and weak boiling of the dioxane until increase in index of refraction stopped (1-2 hours). After cooling, the excess sulfur was filtered off. The residue after distillation of the solvent was a yellow, homogeneous liquid from which after standing for several days sulfur precipitated. The product freed from sulfur (11.9 g, 85%) was the practically pure monoester, d_4^{20} 1.1760, n_D^{20} 1.4951. According to the literature [1], d_4^{20} 1.1758, n_D^{20} 1.4957.

Found %: S 22.98; P 21.90. equiv. 144.9. $\text{C}_3\text{H}_5\text{O}_2\text{SP}$. Calculated %: S 22.87; P 22.10. Equiv. 140.2.

Mixed with sodium ethylate, the monoester was converted to the sodium salt, which after recrystallization from petroleum ether had m.p. 215-216°. According to the literature [16], m.p. 216-218°.

To a solution of 0.05 mole of sodium ethylate (from 1.15 g sodium and 25 ml of anhydrous ethanol) was added 0.05 mole of the unpurified monoethyl ester of methylthiophosphinic acid, and then 0.07 mole of ethyl bromide. The reaction mass was boiled with stirring for three hours, after which most of the alcohol was distilled off in a low vacuum. To the residue was added 40 ml of benzene and water to solution of the salt. The benzene solution was dried over magnesium sulfate and distilled. We obtained 4.8 g (57%) of O-ethyl-S-ethyl methylphosphonate.

*In calculating the molecular refraction of monoalkylphosphonites Kosolapoff [11] without basis used a value of AR^{P} of 4.5, that is, the average value for AR^{P} in dialkylphosphites.

**In a number of pentavalent phosphorus compounds when the alkoxyl group is replaced by an alkyl radical the value of AR^{P} also increases by 0.52 [13, 14].

B.p. 92-93° (9 mm), n_D^{20} 1.4787, d_4^{20} 1.0942. According to the literature [16], b.p. 87-88° (7 mm), n_D^{20} 1.4768, d_4^{20} 1.0951.

Under analogous conditions by alkylation of sodium monoethoxymethylthiophosphonate with butyl bromide we obtained 56% of O-ethyl-S-butyl methylphosphonate.

B.p. 112-114° (9 mm), n_D^{20} 1.4815, d_4^{20} 1.0454.

Found %: S 16.38; P 15.51. $C_7H_{17}O_2SP$. Calculated %: S 16.29; P 15.78.

Monobutylester of methylthiophosphinic acid. It was obtained with a yield of 82.5% from 0.05 mole of the monobutyl ester of methylphosphinous acid and 0.075 g-atom of sulfur in 25 ml of dioxane under conditions described for the ethyl homolog; n_D^{20} 1.4925, d_4^{20} 1.1067.

Found %: S 19.39. Equiv. 174.6. $C_6H_{13}O_2SP$. Calculated %: S 19.01; equiv. 168.1.

Sodium salt had m.p. 193-194° (from petroleum ether).

Found %: S 16.70; P 16.12. $C_5H_{12}O_2SPNa$. Calculated %: S 16.81; P 16.30.

Monohexyl ester of methylthiophosphinic acid. It was obtained with a yield of 89% by the analogous process from 0.05 mole of the monohexyl ester of methylphosphinous acid and 0.075 g-atom of sulfur in 30 ml of dioxane; n_D^{20} 1.4918, d_4^{20} 1.0560.

Found %: S 16.90; P 15.41. Equiv. 208.1. $C_7H_{17}O_2SP$. Calculated %: S 16.31; P 15.80. Equiv. 196.2.

Sodium salt, m.p. 161-163° (from petroleum ether).

Found %: S 14.51; P 14.07. $C_7H_{16}O_2SPNa$. Calculated %: S 14.65; P 14.20.

Reaction of monoethyl ester of methylphosphinous acid with sulfur in ether. a) A mixture of 0.05 mole of monoethoxymethylphosphonite, 0.07 g-atom of powdered sulfur, and 25 ml of absolute ether was heated in a sealed tube at 100° for 5.5 hours. The index of refraction of the solution was practically unchanged. The starting product was recovered by filtration and distillation.

b) To a mixture of 0.05 mole of monoethyl methylphosphonite and 0.055 g-atom of sulfur in 15 ml of absolute ether was added dropwise with stirring a solution of 0.05 mole of triethylamine in 5 ml of the same solvent; weak

Compound	B.p. (pressure in mm)	n_D^{20}	d_4^{20}	Empirical formula	Found		Calculated	
					% P	MR _D	% P	MR _D *
$CH_3-P(=O)(OC_2H_5)_2$	70° (15)	1.4221	1.0511	$C_5H_{11}O_2P$	28.33	26.11	28.70	26.03
$CH_3-P(=O)(OC_3H_7)_2$	84 (15)	1.4265	1.0305	$C_6H_{13}O_2P$	25.15	30.39	25.38	30.65
$CH_3-P(=O)(OC_3H_7-iso)_2$	69-70 (11)	1.4209	1.0117	$C_6H_{13}O_2P$	25.20	30.58	25.38	30.65
$CH_3-P(=O)(OC_4H_9)_2$	88-89 (10)	1.4332	0.9967	$C_7H_{15}O_2P$	22.32	35.45	22.74	35.26
$CH_3-P(=O)(OC_4H_9-iso)_2$	75-76 (8)	1.4270	0.9880	$C_7H_{15}O_2P$	22.40	35.34	22.74	35.26
$CH_3-P(=O)(OC_5H_{11})_2$	106-107 (15)	1.4330	0.9825	$C_8H_{17}O_2P$	20.33	39.68	20.62	39.88
$CH_3-P(=O)(OC_5H_{11}-n)_2$	103-104 (6)	1.4371	0.9592	$C_7H_{17}O_2P$	18.57	44.72	18.85	44.50

* Value of AR^P taken equal to 5.02.

heating occurred. The reaction mass was heated to boiling until solution of the sulfur took place. After cooling to -50° the ether layer was separated with a siphon, and the residue with good cooling was treated with 5 ml of concentrated hydrochloric acid. Solid ammonium chloride was added to the mixture to saturation and the solution was extracted with benzene. After distillation of the solvent in a vacuum, the residue (4.5 g, 64.4%) was sufficiently pure monoethyl ester of methylthiophosphinic acid, n_D^{20} 1.4967, d_4^{20} 1.1754.

Found: Equiv. 142.5. $C_3H_5O_2SP$. Calculated: Equiv. 140.2.

The sodium salt obtained as described above had m.p. 215-217°.

Monoesters of methylphosphinous acid (typical process). To a solution of 0.5 mole of methyldichlorophosphine in 300 ml of absolute ether with stirring and cooling was added a solution of 1.0-1.2 mole of anhydrous alcohol and 0.5 mole (without excess!) of triethylamine in 100 ml of the same solvent. For completion of the reaction the mixture was heated for 30-40 minutes so that the ether boiled weakly. During the whole process dry nitrogen or carbon dioxide was passed through the reaction apparatus. After cooling (it was best to allow the reaction mass to stand overnight), the amine hydrochloride was filtered off, the solvent was distilled from the filtrate, and the residue was distilled in a vacuum in a current of inert gas. The yields of monoalkylphosphonites (table) were 75-90%.

SUMMARY

1. It is shown that in dioxane solution monoalkoxymethylphosphonites add sulfur with formation of monoesters of methylthiophosphonic acid; in ether the reaction occurs only in the presence of a base.
2. The reaction of methyldichlorophosphine with alcohols and tertiary amines at mole ratio 1: 2: 1 respectively, gives good yields of monoesters of methylphosphonous acid.

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STUDIES IN THE IMIDAZOLE SERIES

IX. THE ACTION OF BROMOACETIC ACID ON ESTERS OF 2-MERCAPTOIMIDAZOLE CARBOXYLIC ACIDS

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We previously studied the action of α -haloketones and α -haloaldehydes on 2-mercaptoimidazole [1, 2]; here there was alkylation of the 2-mercaptoimidazoles on the mercapto group. It was established that cyclization of 2- β -ketoalkyl-(aryl)-mercaptoimidazoles to imidazo-(2,1-b)-thiazoles took place with much more difficulty than the formation of derivatives of 2-aminothiazole in the reaction of thiourea with α -halocarbonyl compounds.

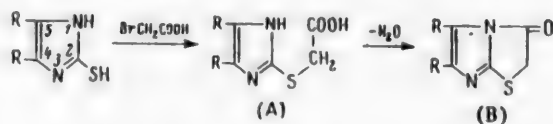
In continuing this work it is interesting to study the action of α -haloacids on 2-mercaptoimidazole and to compare the results with the action of α -haloacids on thiourea. It is known that thiourea reacts easily with chloroacetic acid, forming 2-imino-4-thiazolidone (pseudothiohydantoin) [3-5]. Carrying out the reaction at room temperature permits isolation of an intermediate product, formamidinomercaptoacetic (pseudothiohydantoic) acid [6, 7], which when heated splits out a molecule of water and cyclizes to pseudothiohydantoin [7].

As the objects for study, presenting both chemical and biological interest, we chose esters of 2-mercaptoimidazole carboxylic acid and bromoacetic acid.

The methyl and ethyl esters of 2-mercaptoimidazole-5(4)-carboxylic acid have been described before [2] as have the diethyl ester of 2-mercaptoimidazole-4,5-dicarboxylic acid and the acid itself [8]. We incidentally synthesized imidazole-4,5-dicarboxylic acid by saponifying diethyl imidazole-4,5-dicarboxylate. This method has a number of advantages compared to the others described in the literature [9-11] for preparing it, since the substance is obtained in satisfactory yield at all stages and is of high quality even without purifying the intermediate products.

Due to the difficult solubility of the starting imidazoles in water, and also the danger of hydrolysis of the ester group, the reaction of bromoacetic acid with diethyl 2-mercaptoimidazole-4,5-dicarboxylate and methyl and ethyl 2-mercaptoimidazole-5(4)-carboxylates was carried out in the corresponding alcohols (methanol or ethanol).

By analogy with the action of chloroacetic acid on thiourea, 2-mercapto-4,5-dihydroimidazole [12-14], and 2-mercaptobenzimidazole [12-15], we could expect formation of imidazolyl-2-mercaptoacetic acid (A) or the products of its cyclization, imidazo-(2,1-b)-3-thiazolidones (B).

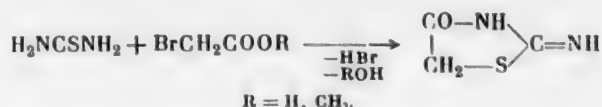


However, in the cases which we studied, due to the catalytic effect of the hydrogen bromide evolved in the reaction there was esterification of the acid (A) and formation in good yield of the hydrobromides of the methyl and ethyl esters of imidazolyl-2-mercaptoacetic acid.

The structure of the resulting compounds was shown in the case of synthesis of the dimethyl ester of 5(4)-carboxyimidazolyl-2-mercaptoacetic acid from methyl bromoacetate. Hydrolysis of the resulting ester in acid or alkaline medium led to complete saponification of all ester groups and formation of the corresponding di- and tricarboxylic acids of the imidazole series. The structure of one of these, 4,5-dicarboxyimidazolyl-2-mercaptoacetic

acid, was confirmed by its synthesis from 4,5-dicarboxy-2-mercaptoimidazole and bromoacetic acid in a water medium.

In distinction from the cyclic derivatives of thiourea, 2-mercaptoimidazoles, unsubstituted thiourea in reaction with bromoacetic acid or its methyl ester under analogous conditions (carrying out the reaction in methanol) did not form the methyl ester of pseudothiohydantonic acid, but its cyclization product, pseudothiohydantoin.



EXPERIMENTAL

Diethyl ester of 2-mercaptoimidazole-4,5-dicarboxylic acid (I). This was prepared by the method of Jones [8] with the difference that in the Claisen reaction we used benzene, not ether, as the solvent. Long yellow prisms (from dichloroethane) or short, thick prisms (from ethanol or water) with m.p. 203.5-204.5° (with foaming); according to [8], m.p. 204-205°; the substance is easily soluble with heat in the lower alcohols, acetone, dichloroethane, chloroform, ethyl acetate, dioxane, and glacial acetic acid; very poorly soluble in methylene chloride, carbon tetrachloride, benzene, ether, ligroin, and water.

2-Mercaptoimidazole-4,5-dicarboxylic acid (II). Obtained by the method of Jones [8]. Yield of technical product 91.3%, m.p. 244-245° (decomposition). Yellow or orange crystals, very little soluble with heat in most organic solvents, easily soluble in hot water with formation of a colorless solution. The compound crystallizes in a yellow (anhydrous) and an orange (dihydrate) form. After recrystallization from water it forms short, thick, orange prisms, and from aqueous alcohol, fan shaped plates of dihydrate which darkens at 272-275° and melts at 292-295° (decomposition).

Found %: C 26.46; H 2.25; N 12.64; S 14.40. C₅H₄O₄N₂S · 2H₂O. Calculated %: C 26.79; H 3.59; N 12.49; S 14.30.

In recrystallization of the dihydrate from dilute hydrochloric acid, from water with addition of several drops of hydrochloric acid to the cold solution, or on simple washing of the dihydrate on the filter with dilute hydrochloric acid, the anhydrous yellow form results, with m.p. 245-246° (decomposition); according to [8], m.p. 251-252°.

Found %: C 32.57; H 2.11; N 14.74; S 17.25. C₅H₄O₄N₂S. Calculated %: C 31.92; H 2.14; N 14.89; S 17.04.

Diethyl ester of imidazole-4,5-dicarboxylic acid (III). Prepared by the method of Jones [8]. The yield of technical product with m.p. 146-148° was 86-90%. After recrystallization from water, long, colorless prisms with m.p. 151-152° (according to [8], m.p. 151-152°), easily soluble in the majority of organic solvents and hot water, soluble with difficulty in cold water.

Imidazole-4,5-dicarboxylic acid (IV). A mixture of 6.8 g of ester (III) and 40 ml of 24% aqueous sodium hydroxide was heated in a beaker on a water bath for 2.5 hours. The dry residue was dissolved in hot water, filtered, and neutralized with hydrochloric acid to an acid reaction to Congo. The resulting precipitate was filtered off, washed with water, and dried. We obtained 5.3 g (93%) of substance with m.p. 254-267° (melting with decarboxylation in the range of 1°). For analysis the substance was converted to the sodium salt [11] (long, colorless needles from water, not melting at 290°, easily soluble in hot water, difficultly soluble in cold water), which was converted to the acid by acidification with hydrochloric acid. Colorless, fine prisms with m.p. 255-267° (in the range 0.5-1°, decomposition) (according to [11], m.p. 288°), almost insoluble in water and most organic solvents.

Found %: C 38.02; H 2.83; N 17.95. C₅H₄O₄N₂. Calculated %: C 38.47; H 2.58; N 17.95.

Methyl ester of 5(4)-carbomethoxyimidazolyl-2-mercaptoacetic acid hydrobromide (V). a) A solution of 1.35 g of the methyl ester of 2-mercaptoimidazole-5(4)-carboxylic acid [2] and 1.24 g of bromoacetic acid in 10 ml of anhydrous methanol was boiled for one hour and ten minutes, after which the solvent was distilled off in a vacuum. The colorless crystalline residue was washed on the filter with ethyl acetate, then with ether, and dried. We obtained 2.48 g (93.6%) of substance with m.p. 138-139° (decomposition). After crystallization from a mixture of carbon tetrachloride and methanol, colorless prisms with m.p. 141.5-142.5° (decomposition), easily soluble in water, aqueous

solutions of sodium acetate, lower alcohols, acetone and acetonitrile (in the last two, with heating); insoluble in ether, ethyl acetate, carbon tetrachloride, chloroform, and benzene.

Found %: C 30.57; H 3.32; N 8.54; S 10.59; Br 25.07. $C_8H_{10}O_4N_2S \cdot HBr$. Calculated %: C 30.88; H 3.56; N 9.00; S 10.30; Br 25.68.

b) A solution of 0.21 g of methyl ester of 2-mercaptoimidazole-5(4)-carboxylic acid and 0.26 g of methyl bromoacetate in 3 ml of methanol was boiled for one hour, after which the solvent was distilled off in a vacuum. The residual oily substance in the flask crystallized when ground with ethyl acetate. The crystals were filtered off, washed with ethyl acetate, then with ether, and dried. We obtained 0.38 g (95.1%) of substance with m.p. 141-142° (decomposition). A sample mixed with the substance obtained by method "a" gave no melting point depression.

Ethyl ester of 5(4)-carbethoxyimidazolyl-2-mercaptoacetic acid hydrobromide (VI). A solution of 1 g of the ethyl ester of 2-mercaptoimidazole-5(4)-carboxylic acid [2] and 0.85 g of bromoacetic acid in 10 ml of anhydrous ethanol was boiled for 45 minutes, after which the solvent was distilled off in a vacuum. The colorless precipitate was filtered, washed with ether, and dried. We obtained 1.6 g (81.2%) of substance with m.p. 119-121°. For analysis the substance was purified by reprecipitation with ether from an acetone solution which had been treated with charcoal. Colorless crystals with m.p. 120-121°, analogous to substance V in its solubility.

Found %: C 35.04; H 4.23; N 8.36; S 9.58; Br 23.13. $C_{10}H_{14}O_4N_2S \cdot HBr$. Calculated %: C 35.41; H 4.46; N 8.26; S 9.45; Br 23.56.

5(4)-Carboxyimidazolyl-2-mercaptoacetic acid (VII). a) A solution of 0.95 g of the ester salt (V) in 3 ml of 36% hydrochloric acid was boiled for three hours, after which the hydrochloric acid was evaporated dry in a beaker on a water bath, the dry crystalline residue was washed with acetone and dried. We obtained 0.66 g (97%) of substance with m.p. 198-199° (decomposition). Fine, colorless prisms (from water) with m.p. 210-210.5° (decomposition), difficultly soluble in hot water, very little soluble in cold water and most organic solvents, easily soluble in hydrochloric acid and solutions of bases.

Found %: C 35.80; H 3.18; N 13.58; S 15.86. $C_6H_6O_4N_2S$. Calculated %: C 35.64; H 2.99; N 13.86; S 15.86.

b) A solution of 0.38 g of compound (VI) in 2.5 ml of 36% hydrochloric acid was boiled for three hours, after which it was treated as in experiment "a". We obtained 0.22 g (97.3%) of substance with m.p. 203-204° (decomposition) and after recrystallization from water, colorless prisms with m.p. 210-210.5° (decomposition), giving no melting point depression with the substance prepared by method "a".

c) A solution of 0.8 g of compound (V) in 3 ml of 25% aqueous sodium hydroxide was boiled for one hour, after which to it was added 2.5 ml of 36% hydrochloric acid, and the solution was evaporated dry. The dry residue was washed with water, then with acetone, and was dried. We obtained 0.31 g (57%) of substance with m.p. 209-210° (decomposition) which gave no depression of the melting point mixed with the substance obtained by method "a".

Ethyl ester of 4,5-dicarbethoxyimidazolyl-2-mercaptoacetic acid hydrobromide (VIII). A solution of 2.44 g of ester (I) and 1.46 g of bromoacetic acid in 10 ml of anhydrous ethanol was boiled for 30 minutes, after which it was cooled, and the solvent was distilled off in a vacuum. The remaining thick oil crystallized when ether was added. The crystals were filtered off, washed with ether, and dried. We obtained 3.58 g (87.1%) of a substance with m.p. 135-136°. Long, colorless prisms or needles (from acetone) with m.p. 139-140°, analogous in solubility to compounds (V) and (VI).

Found %: C 37.80; H 4.84; N 6.83; S 7.61; Br 18.96. $C_{13}H_{18}O_6N_2S \cdot HBr$. Calculated %: C 37.96; H 4.66; N 6.81; S 7.79; Br 19.43.

4,5-Dicarboxyimidazolyl-2-mercaptoacetic acid (IX). a) A solution of 0.78 g of acid (II) and 0.51 g of bromoacetic acid in 10 ml of water was boiled for 35 minutes, and the precipitate which separated after cooling was filtered, washed with water, then with acetone, with ether, and was dried. We obtained 0.72 g (78.3%) of substance with m.p. 215-216° (decomposition). The colorless prisms of monohydrate (from water, ethanol, methanol, or acetic acid) with m.p. 215-216° (decomposition) were well soluble with heating in water, lower alcohols, and dioxane; difficultly soluble in acetone and glacial acetic acid; insoluble in ether, benzene, chloroform, dichloroethane, carbon tetrachloride, and ethyl acetate.

Found %: C 31.81; H 3.11; N 10.67; S 12.37; H_2O 8.10 (Fischer's method) $C_7H_6O_6N_2S \cdot H_2O$. Calculated %: C 31.82; H 3.05; N 10.60; S 12.14; H_2O 6.82.

b) A mixture of 0.47 g of ester (VIII) and 3 ml of 25% water solution of sodium hydroxide was boiled for one hour, after which the solution was diluted with 10 ml of water and neutralized with 36% hydrochloric acid to an acid reaction to Congo. The precipitate which separated was filtered off, washed with water, then with acetone and with ether, and was dried. We obtained 0.25 g (83.3%) of colorless crystals with m.p. 214-215° (decomposition) which gave no melting point depression with the substance synthesized by method "a".

2-Imino-4-thiazolidone (pseudothiohydantoin, X). a) A mixture of 7.61 g of thiourea and 9.45 g of chloroacetic acid in 45 ml of glacial acetic acid was carefully heated to the end of the stormy reaction, after which it was boiled for 30 minutes; a colorless precipitate came down. After cooling the reaction mass we filtered the precipitate, washed it with glacial acetic acid, then with ether, and dried it. We obtained 14.8 g (97%) of hydrochloride of substance (X) with m.p. 210-220° (decomposition). Addition of sodium acetate to the water solution of the hydrochloride gave the base (X): colorless long prisms (from water) with decomposition at 200-210° (according to [7], decomposition point about 200°), soluble in hydrochloric and glacial acetic acid, sodium hydroxide solution, and hot water, slightly soluble in cold water, almost insoluble in most organic solvents.

b) A mixture of 7.61 g of thiourea and 13.9 g of bromoacetic acid in 45 ml of glacial acetic acid was heated and treated as described above. We obtained 18.93 g (88.5%) of hydrobromide of compound (X) with m.p. 210-215°. Colorless prisms (from ethanol or methanol), soluble in water and lower alcohols (with heating), difficultly soluble in glacial acetic acid. Part of the hydrobromide was dissolved in warm water and sodium acetate was added to the solution. The colorless prisms which precipitated were filtered, washed with water, ethanol, and ether, and then were dried. We obtained base (X) with decomposition point 203-208°. A sample mixed with (X) prepared by method "a" had decomposition point 203-209°.

c) A solution of 3.8 g of thiourea and 7 g of bromoacetic acid in 50 ml of methanol was boiled for 70 minutes with simultaneous distillation of the solvent, and at the end there was precipitation of a colorless, crystalline residue. Ether was added to the residue; the precipitate was filtered off, washed with ether, and dried. We obtained 9.74 g (90.6%) of hydrobromide of compound (X) with decomposition point 210-212°. A sample mixed with the hydrobromide obtained by method "b" gave no melting point depression. Part of the hydrobromide was dissolved in warm water and decomposed with sodium acetate. Colorless prisms separated with decomposition point 200-210°, shown identical with compound (X) obtained by methods "a" and "b".

d) A solution of 2 g of thiourea and 4.2 g of methyl bromoacetate in 25 ml of methanol was boiled for 15 minutes with simultaneous distillation of the solvent (at the end in a vacuum). The crystalline precipitate was washed with ether, filtered, and dried. We obtained 5.36 g (98.8%) of substance with decomposition point 210-214°. A sample mixed with hydrobromide of (X) prepared by method "b" gave no depression of the decomposition point. Part of the hydrobromide was treated with sodium acetate as in the previous experiments. We obtained colorless prisms of the base (X) with decomposition point 200-210°. A sample mixed with (X) prepared by method "a" gave no depression of the decomposition point.

SUMMARY

We have studied the action of bromoacetic acid on esters of 2-mercaptoimidazole-5(4)-carboxylic and 2-mercaptoimidazole-4,5-dicarboxylic acids. We have shown that when the reaction is carried out in alcohol there are formed esters of 5(4)-carbalkoxy- and 4,5-dicarbalkoxyimidazolyl-2-mercaptoacetic acid. Saponification of these esters gave the previously undescribed 5(4)-carboxy- and 4,5-di-carboxyimidazolyl-2-mercaptoacetic acids.

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CONDENSATIONS OF HETEROCYCLIC POLYMETHYLENE DERIVATIVES BASED ON LACTAMS

III. SYNTHESIS OF 1,2-PENTAMETHYLENEPYRIMIDINES

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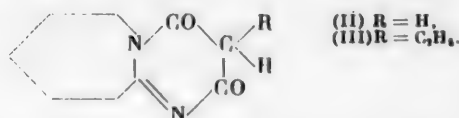
As was shown in previous communications [1, 2] O-methylcaprolactim is very easily condensed, because of the CH_2O group, with compounds which have a mobile hydrogen atom on carbon or nitrogen [3]. The resulting

primary condensation products due to lactim-lactam tautomerism $(\text{CH}_2)_5 \begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{C}=\text{X} \end{array} \rightleftharpoons (\text{CH}_2)_5 \begin{array}{c} \text{NH} \\ | \\ \text{C}=\text{X} \end{array}$ (where

$\text{X} = \text{RR}_4\text{C}$ or NR) are then easily cyclized into five-membered heterocycles (imidazoles, triazoles, tetrazoles).

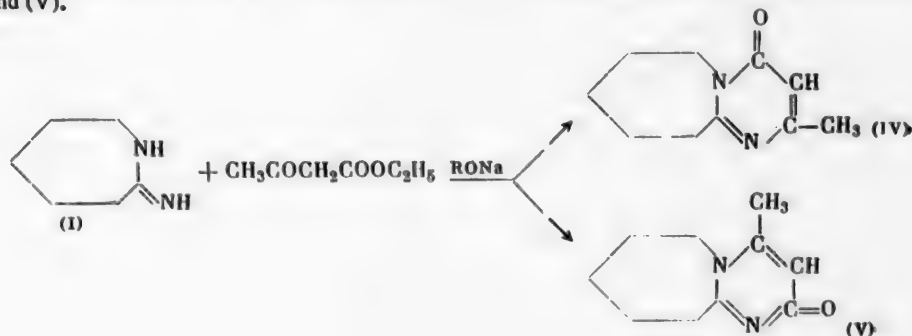
We would expect that the cyclic amidine (I) formed from O-methylcaprolactim and ammonium salts would also condense easily with β -dicarbonyl compounds with the formation of 1,2-pentamethylenepyrimidines, analogous to the condensation of 2-aminopyrimidine with β -dicarbonyl compounds with formation of oxypyrimidines [4].

Experiments fully confirmed our idea: In the condensation of caprolactam amidine (I) sulfate in the presence of sodium ethylate with malonic and ethylmalonic esters we obtained good yields of 4,6-dioxo-1,2-pentamethylene-1,4,5,6-tetrahydropyrimidines (II) and (III).



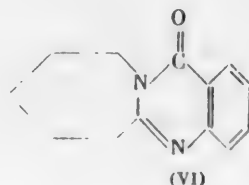
Attempts at condensation under these conditions of the amidine (I) with diethyl or phenylethylmalonic esters did not give positive results, evidently because of the impossibility of enolization of the disubstituted malonic ester [5]. We were also unsuccessful in experiments with the alkylated pyrimidine (III) and also the diamide of phenylmalonic acid with ethyl bromide in the presence of sodium alcoholate. In this case there was a passivating action of the two carbamide groups on the mobility of the α -hydrogen atom.

As a representative of the monooxypyrimidines we have synthesized 1,2-pentamethylene-4-methyl-6-oxo-1,6-dihydropyrimidine by condensation of amidine (I) with acetoacetic ester in the presence of sodium alcoholate. Since here pyrimidine cyclization can occur in two directions, we ran a countersynthesis of one of the possible reaction products (IV) and (V).

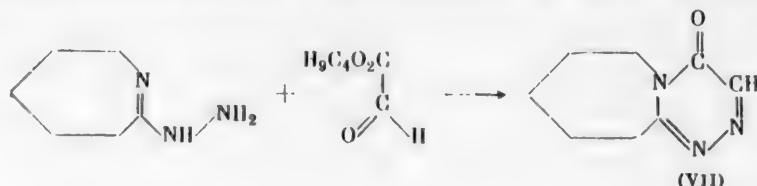


Compound (IV) was synthesized by condensation of O-methylcaprolactim with β -aminocrotonic ester. It was completely identical with the reaction product from amidine (I) with acetoacetic ester.

A more complex 6-oxopyrimidine was obtained in the reaction of O-methylcaprolactim with anthranilic acid in alcohol medium. This condensation occurs very easily with formation of 2,3-pentamethylene-3,4-dihydro-4-quinazoline (VI)



There may be interest in the biological properties of these compounds. In this connection we synthesized from 2-hydrazino- $\Delta^{1,2}$ -homopiperidine [1] and butyl glyoxylate the stereoisomer of the oxopyrimidines, an analog of 6-azauracil which has an anticancer action [6], 3,4-pentamethylene-4,5-dihydro-1,2,4-triazin-6-one (VII).



We are continuing the study of the synthesis of heterocycles from caprolactam.

EXPERIMENTAL

Sulfate and nitrate of caprolactam amide (I). A mixture of 25.4 g of O-methylcaprolactim and 13.5 g of anhydrous ammonium sulfate was shaken for 43 hours in 50 ml of anhydrous methanol at room temperature. During the reaction there was a change in consistency of the precipitate. Then the reaction mass was partly evaporated; the precipitate was filtered off, washed with a small amount of alcohol, and dried; the yield of caprolactam amidine sulfate was 31.45 g (97.67%), m.p. 210-212° (dark melt). For analysis 0.25 g of substance was recrystallized from a mixture of 20 ml of anhydrous alcohol and 20 ml of absolute ether: platelets, m.p. 223-225° (decomposition).

Found %: S 9.76. $C_6H_{12}N_2 \cdot \frac{1}{2}H_2SO_4$. Calculated %: S 9.93.

Analogously from O-methylcaprolactim and ammonium nitrate we obtained caprolactam amidine nitrate, m.p. 128-129° with a yield of 96.87%.

Found %: C 40.91; H 6.86; N 24.02. $C_6H_{12}N_2 \cdot HNO_3$. Calculated %: C 41.14; H 7.42; N 24.00.

4,6-Dioxo-1,2-pentamethylene-1,4,5,6-tetrahydropyrimidine (II). To C_2H_5ONa (prepared from 5 g of Na and 150 ml of anhydrous alcohol) was added 18 g of malonic ester and then 16.1 g of caprolactam amidine bisulfate; the mass was boiled for 30 minutes and a precipitate gradually came down; the mixture was evaporated dry and on the residue, with ice cooling, was poured 50 ml of water, and the resulting solution was acidified with 20% hydrochloric acid to a pH about 6. The precipitate was filtered off and washed with chloroform; the mother liquor was extracted with chloroform. The chloroform solutions were combined, dried with sodium sulfate, and evaporated; we obtained 14.7 g (81.5%) of substance with m.p. 180-187°; after crystallization of 2.2 g of substance from 20 ml of alcohol, m.p. 218-220° (platelets). The substance was difficultly soluble in ether, acetone, benzene, and ethyl acetate; easily so in chloroform, alcohol, and water; it was also dissolved by a 5% solution of bicarbonate.

Found %: N 15.34, 15.79. M (titration) 183. $C_9H_{12}O_2N_2$. Calculated %: N 15.55. M 180.

4,6-Dioxo-1,2-pentamethylene-5-ethyl-1,4,5,6-tetrahydropyrimidine (III). To CH_3ONa (prepared from 5 g of Na in 150 ml of 99.9% CH_3OH) was added 20 g of ethylmalonic ester and 16.1 g of caprolactam amidine sulfate; the mixture was boiled for 1.5 hours, evaporated, and treated as in the previous experiment; we obtained 13.7 g (65.87%) of substance with m.p. 202-206°; after crystallization of 4 g from a mixture of 25 ml of benzene and 1.5 ml of

methanol, m.p. 213-215° (tetrahedra). The substance was easily soluble in methanol and chloroform, soluble with difficulty in water, acetone, ethyl acetate, and ether; it did not evolve CO₂ from a bicarbonate solution.

Found %: N 13.40. C₁₁H₁₆O₂N₂. Calculated %: N 13.45.

1,6-Dihydro-1,2-pentamethylene-4-methyl-6-oxypyrimidine (IV). a) To a solution of C₂H₅ONa (prepared from 5 g Na and 150 ml of anhydrous alcohol) was added 14 g of acetoacetic ester and 16.1 g of amidine sulfate; the mixture was boiled for one hour; to the residue cooled with ice was added 40 ml of cold water, and the resulting solution was extracted with chloroform; the extract was dried with sodium sulfate and evaporated; we obtained 14.2 g (79.77%) of substance with m.p. 83-86°; after crystallization from ether, m.p. 84.5-86.5°. The substance was easily soluble in water (pH about 8), alcohol, and chloroform; more difficultly in ether, benzene, and ethyl acetate.

Found %: N 15.84. C₁₀H₁₄ON₂. Calculated %: N 15.84.

b) To a suspension of 11 g of β-aminocrotonic ester [7] in 5 ml of anhydrous alcohol during ten minutes was added dropwise 12 ml of O-methylcaprolactam; with further stirring the reaction mass was heated to 28° and everything dissolved; with further stirring for 45 minutes the temperature fell to 21°. The mixture was heated at 80° for 30 minutes and evaporated. The residue was dissolved in ether and precipitated with n-hexane; 5 g of substance precipitated, and after crystallization from ether we obtained 2.5 g with m.p. 84-86°; a sample mixed with that obtained by process "a" gave no melting point depression.

From the mother liquors after treatment with a 21% alcoholic solution of HCl we obtained 6 g of hydrochloride of 1,6-dihydro-1,2-pentamethylene-4-methyl-6-oxypyrimidine, which after crystallization from anhydrous alcohol had m.p. 231-233°. Total yield 48.8%.

Found %: Cl 16.54, 16.58. C₁₀H₁₄ON₂·HCl. Calculated %: Cl 16.55.

2,3-Pentamethylene-3,4-dihydroquinazol-4-one (VI). To a suspension of 14 g of anthranilic acid in 20 ml of anhydrous alcohol in the course of 10 minutes was added dropwise 13 g of O-methylcaprolactim; there was a rise in temperature in the reaction mass to 45°. The resulting solution was cooled with water and after 1.5 hours stirring was evaporated in a vacuum; the residue (21.6 g, about 100%) after standing about 12 hours crystallized. After crystallization of 1.9 g of substance from a mixture of 30 ml of ether and 1 ml of alcohol, m.p. 95-96.5°.

2,3-Pentamethylene-3,4-dihydroquinazol-4-one was difficultly soluble in water, dilute alkali, and ether, and easily so in alcohol, chloroform, benzene, acetone, and ethyl acetate.

Found %: N 13.01. C₁₃H₁₄ON₂. Calculated %: N 13.08.

2,3-Pentamethylene-3,4-dihydroquinazol-4-one hydrochloride was obtained by treating the base as a 15% alcoholic solution with an alcoholic solution of HCl; platelets with m.p. 209-211°.

Found %: N 11.16; Cl 13.84. C₁₃H₁₄ON₂·HCl. Calculated %: N 11.17; Cl 14.17.

3,4-Pentamethylene-4,5-dihydro-1,2,4-triazin-6-one (VII). To a solution of 13 g of butyl glyoxylate [8] in 50 ml of anhydrous alcohol was added gradually with ice cooling 12.7 g of 2-hydrazino-Δ^{1,2}-homopiperidine by drops; the mixture was boiled for one hour, then evaporated; the residue was dissolved in 20 ml of water; the water solution was extracted with chloroform; the extract was dried with sodium sulfate and evaporated; we obtained 6 g (36.36%) of substance with m.p. 87-91°; after two crystallizations from ether, m.p. 98-100° (large prisms).

The substance was easily soluble in water, methanol, acetone, benzene, chloroform, and ethyl acetate, more difficultly so in ether; it did not reduce ammoniacal silver oxide solutions.

Found %: C 57.86; H 6.61; N 25.16. C₈H₁₁ON₃. Calculated %: C 58.18; H 6.66; N 25.45.

SUMMARY

1. Caprolactam amidine, easily formed from O-methylcaprolactim by the action of ammonium salts, can undergo condensation with 1,3-dicarbonyl compounds giving 1,2-pentamethylene-monooxo- or dioxohydropyrimidines. The 5-alkyl analogs of uracil thus obtained cannot be further alkylated.

2. Caprolactam amidine reacts smoothly with anthranilic acid, forming 2,3-pentamethylene-3,4-dihydroquinazol-4-one. The analogous 2-hydrazino-Δ^{1,2}-homopiperidine in condensation with butyl glyoxylate easily gives 3,4-pentamethylene-4,5-dihydro-1,2,4-triazin-6-one.

3. These facts indicate the easy ability of caprolactam amidine to react in the tautomeric diimino form.

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REACTIONS OF AROMATIC SULFONIC ESTERS

XI. ALKALINE AND NEUTRAL HYDROLYSIS OF NITRO-SUBSTITUTED PHENYL BENZENESULFONATES

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Alkylsulfonates and arylsulfonates differ considerably from each other in reactivity of bonds. While in alkylsulfonates the reaction of nucleophilic substitution occurs with rupture of the O-Alk bond [1-3], in the arylsulfonates the S-O bond is ruptured. The study of the effect of the nature and position of the substituent in the acid [4, 5] and in the phenol part of the arylsulfonate on rate of hydrolysis [6, 7] which we carried out showed for them the acyl-oxygen S_N2 mechanism. This mechanism was confirmed by our studies of neutral and alkaline hydrolysis of nitro- and dinitrophenyl benzenesulfonates in the presence of H_2O^{18} [8]. Thus, we can consider it to be established that neutral and alkaline hydrolysis of unsubstituted and substituted aryl sulfonates proceeds according to the acyl-oxygen mechanism.

While the use of the isotope method permits us to judge the point of rupture of the bond, the study of the effect of structural factors on the kinetics of the process permits a judgement of whether this reaction takes place by mechanism S_N1 or S_N2 ; gives an indication of the state of the molecule at the moment of reaction; and, finally, permits a quantitative estimation of the reactivity of the molecule depending on the nature and position of the substituent.

In carrying out the earlier studies we showed that the greatest rate of neutral and alkaline hydrolysis occurred with 2,4-dinitrophenyl benzenesulfonate. Therefore it was interesting to study in detail the reactivity of the dinitro-substituted arylsulfonates and especially to study the effect of position of nitro and chloro substituents in phenyl benzenesulfonate on the rate of neutral and alkaline hydrolysis.

EXPERIMENTAL

We submitted to alkaline and neutral hydrolysis esters of 4-chlorobenzenesulfonic acid and 2,6-dinitrophenol (I), 2,4-dinitrophenol (II), 2,5-dinitrophenol (III), 3,4-dinitrophenol (IV), 2-chloro-3-nitrophenol (VII), 2-nitro-4-chlorophenol (V), 2-chloro-4-nitrophenol (VI); esters of benzenesulfonic acid and 2,4-dinitrophenol (X), 2,6-dinitrophenol (VIII); esters of mesitylenesulfonic acid and 2,4-dinitrophenol (XII), 2,6-dinitrophenol (IX); the ester of p-toluenesulfonic acid and 2,4-dinitrophenol (XI). Most of these esters have not been described in the literature.

Esters (VIII-XI) were obtained* by adding an alcohol solution of the benzenesulfonyl chloride to an alcohol solution of the corresponding phenolate. Reaction took place in an anhydrous medium with heating to 20-40°. Esters (I-VII) were obtained by the method of Ullmann [9], esters (XII) and (IX) by reaction of equimolecular amounts of mesitylenesulfonyl chloride and potassium 2,4- or 2,6-dinitrophenolate. The reaction was carried out in the absence of a solvent with heating for two hours on a water bath at 80-90°. The solid product was washed with water and recrystallized several times from alcohol. The yield of esters was 70-80%. The melting points of the esters and analyses for sulfur are given in Table 1.

Saponification was carried out with alkali in 70% (by volume) aqueous solution of dioxane at 0 and 15° and initial concentration of ester of 0.0031 M and of alkali 0.0084 M. The rate of hydrolysis was measured by titration of excess acid by alkali in the presence of methyl red indicator. A more detailed description of the experimental method is given in [6]. The rate constants of hydrolysis were calculated by an equation of the second order with account of the double consumption of alkali:

*With participation of student G. Elagin.

TABLE 1

Formula	M.p.	% S	
		found	calculated
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,6-(NO ₂) ₂	150—151°	8.78	8.93
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,4-(NO ₂) ₂	115—116	8.80	8.93
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,5-(NO ₂) ₂	126—127	8.63	8.93
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -3,4-(NO ₂) ₂	125—126	9.08	8.93
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2-NO ₂ -4-Cl	91—92	9.08	9.19
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2-Cl-4-NO ₂	102—103	8.92	9.19
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2-Cl-3-NO ₂	125—126	9.02	9.19
C ₆ H ₅ SO ₂ OC ₆ H ₃ -2,6-(NO ₂) ₂	139—140	9.95	9.88
Sym-(CH ₃) ₃ -C ₆ H ₂ SO ₂ OC ₆ H ₃ -2,6-(NO ₂) ₂	165—167	8.91	8.73
C ₆ H ₅ SO ₂ OC ₆ H ₃ -2,4-(NO ₂) ₂	118—119	9.93	9.88
4-CH ₃ -C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,4-(NO ₂) ₂	120—121	9.32	9.47
Sym-(CH ₃) ₃ -C ₆ H ₂ SO ₂ OC ₆ H ₃ -2,6-(NO ₂) ₂	121—122	8.84	8.73

TABLE 2

Alkaline Hydrolysis of 2,6-Dinitrophenyl Benzenesulfonate*

0°				15°			
t (min)	a - 2x	b - x	k	t (min)	a - 2x	b - x	k
0	0.00946	0.00312	—	0	0.00946	0.00312	—
3	0.00548	0.00112	0.824	2	0.00429	0.00053	2.59
8	0.00416	0.00046	0.693	4	0.00372	0.00025	2.01
13	0.00378	0.00027	0.614	5.5	0.00353	0.00015	2.08
k _{average}			0.710	k _{average}			2.22

*Dimensions of k, liter/mole sec.

TABLE 3

Alkaline Hydrolysis of 2-Nitro-4-chlorophenyl 4-Chlorobenzenesulfonate*

0°				15°			
t (min)	a - 2x	b - x	k	t (min)	a - 2x	b - x	k
0	0.00946	0.00281	—	0	0.00946	0.00281	—
13	0.00813	0.00205	0.046	3	0.00794	0.00205	0.202
25	0.00737	0.00167	0.041	10	0.00643	0.00129	0.167
60	0.00605	0.00101	0.038	16	0.00567	0.00091	0.167
k _{average}			0.042	k _{average}			0.179

*Dimensions of k, liter/mole sec.

TABLE 4

Effect of Position of Substituent in Phenyl Benzenesulfonates on Rate of Alkaline and Neutral Hydrolysis*

Formula	Alkaline hydrolysis				Neutral hydrolysis		
	$k_0 \cdot 10^3$	$k_{10} \cdot 10^3$	E	lg pZ	AS [#]	time of heating (in hours)	KOH (in ml)
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,6-(NO ₂) ₂	198)					44	7.45
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,4-(NO ₂) ₂	117)					44	2.8)
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,5-(NO ₂) ₂	702	2310	12400	9.77	-16.41	103	2.0)
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -3,4-(NO ₂) ₂	173	56)	12000	8.85	-21.67	180	1.4)
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,4-(NO ₂) ₂	44	183	14900	10.49	-13.14	180	2.20
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,5-(NO ₂) ₂	37	144	14200	9.97	-15.56	180	—
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,6-(NO ₂) ₂	13	63	16300	11.53	-8.43	180	—
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,4-(NO ₂) ₂	737	220)	11400	8.98	-20.05	44	5.90
4-Cl-C ₆ H ₄ SO ₂ OC ₆ H ₃ -2,6-(NO ₂) ₂	168	631	13800	10.27	-14.17	44	6.30
Sym-(CH ₃) ₂ C ₆ H ₃ SO ₂ OC ₆ H ₃ -2,4-(NO ₂) ₂	318	996	11900	9.92	-19.85	44	2.05
C ₆ H ₅ SO ₂ OC ₆ H ₃ -2,4-(NO ₂) ₂	112	382	12800	9.28	-18.75	44	2.2
Sym-(CH ₃) ₂ C ₆ H ₃ SO ₂ OC ₆ H ₃ -2,4-(NO ₂) ₂	84	306	13600	9.82	-16.19	44	2.45

Not hydrolyzed
Not hydrolyzed* Dimensions: k , liter/mole sec; E, cal/mole; log pZ, liter/mole sec; ΔS^\ddagger , cal/deg mole.

$$\frac{dx}{dt} = k(a - 2x)(b - x)$$

The energy of activation and the exponential factor were calculated from the Arrhenius equation.

Calculation of the entropy of activation [10] was carried out by the formula:

$$\Delta S = -49.19 + 4.575 \lg \frac{k}{T} + \frac{E}{T}$$

The data from several typical experiments on hydrolysis of the ester of 2,6-dinitrophenol and benzenesulfonic acid, and also of 2-nitro-4-chlorophenol and 4-chlorobenzenesulfonic acid are given in Table 2 and Table 3. In Table 4 we give the basic data for the kinetics of the nitro-substituted arylsulfonates studied in the present work.

For the study of the neutral hydrolysis a 0.00016-mole sample of ester was dissolved in 20 ml of 70% aqueous dioxane solution and was heated for a long time (Table 4) in a flask with a reflux condenser. The acid formed as a result of the hydrolysis was titrated with 0.019 N KOH solution in the presence of methyl red. By amount of alkali used we determined the percent of ester hydrolyzed.

DISCUSSION OF RESULTS

Comparison of the rate of hydrolysis of dinitro-substituted and nitrochloro-substituted arylsulfonates (Table 4) allows us to offer a comparative estimate of the effect of nature and position of substituents in the phenol residue on the rate of hydrolysis of arylsulfonates. Esters which contain two nitro groups in the phenol residue are saponified more rapidly than in the nitrochlorophenyl benzenesulfonates. In the study of the effect of position of the nitro groups in monosubstituted esters on the rate of their hydrolysis, we found the following regularity: o-NO₂ > p-NO₂ > m-NO₂ [7].

The study of the effect of introduction of several nitro groups into the phenol part of the ester on rate of alkaline hydrolysis of arylsulfonates allowed us to arrange the nitro groups in the following order:



In this case also the greatest hastening effect is found with substitution in positions 2 and 6. Thus, nitro groups in the ortho position do not show a special effect, which confirms the acyl-oxygen mechanism of hydrolysis of these esters, in which the active reaction center is the sulfur atom of the

sulfonic group. Nitro and chloro substituents in their effect on the rate of hydrolysis are arranged in the order:



Evidently the effect of chlorine as an electronegative substituent is slight and this series is analogous to the series of mononitro derivatives. The observed effect of position of the nitro group in the phenol (with respect to the ester oxygen) on the rate of hydrolysis of nitro- and dinitro-substituted phenyl benzenesulfonates shows that in the acyl-oxygen mechanism of hydrolysis the effect of coupling of the p-electrons of the oxygen with the π -electrons of the benzene ring is of much greater significance for the rate of hydrolysis than is the inductive effect; in the latter case the NO_2 groups would be arranged in the order:



In comparing the effect of nature of substituent on value of k , E , and pZ we do not find the strict regularity which occurs in comparing only one para-substituent. In such a case, this interrelation is complicated not only by change in nature of the substituent but also by its reciprocal position. However, for each separate ester the change in the rate constant depends on energy of activation, and if the latter is decreased, then the rate of reaction is increased. Independent of the temperature factor pZ is increased with increasing activation energy.

The value of the entropy of activation is negative and varies from -13 to -20 cal/deg mole, approaching the value for the entropy of activation of the hydrolysis of benzoic acid esters (-24.9) and differing from that for the reaction of ethyl benzenesulfonate, for which it is -10 cal/deg mole. Such a difference in entropy of activation characterizes the difference in distribution of electron density in the formation of a transitional structure. The low value of the entropy of activation in ethyl benzenesulfonate indicates that in the transitional state of the reaction of its alkaline hydrolysis there is a free, not a tight, structural bond between the ester oxygen and the alkyl carbon. Here in the aryl sulfonates there is a rigid structure dependent on distribution of electron density and change in solvation with formation of the transitional state.

The introduction of a methyl group in benzenesulfonic acid, which lessens the positive charge on the sulfur atom, lessens the rate of hydrolysis (esters X and XI). The introduction of three methyl groups in positions 2, 4, 6 creates a special hindrance in the reaction center (esters X and XII) which decreases the reaction rate to a much lower degree, in spite of expectations. This can be explained by the fact that the benzene ring evidently at the moment of reaction leaves the plane, and the methyl group does not have a special effect on the approaching reagents. The introduction of a NO_2 group in the ortho position with respect to the sulfonic group has a slowing effect compared to the para and meta positions; this shows that in this case the benzene ring does not leave the plane and the o- NO_2 group has a special effect on the approaching reagents [3]. Thus, the departure of the benzene ring of benzenesulfonic acids from a plane occurs only in the presence of a substituent with a large atomic radius.

Neutral hydrolysis was tested with esters which show the greatest rate of alkaline hydrolysis. Of the dinitro-substituted esters, the lowest rate of hydrolysis is in esters of 3,4-dinitrophenol. Nitrochloro-substituted esters, except for esters of 2-nitro-4-chlorophenol, are not hydrolyzed by water. Esters which contain a methyl group in the benzenesulfonic portion are hydrolyzed faster than the corresponding nonmethylated esters (in alkaline hydrolysis the reverse order is found). This permits us to suggest the possibility of a change in mechanism of hydrolysis, but this requires experimental confirmation (for example, by the isotope method).

SUMMARY

1. We have prepared ten arylsulfonates not described in the literature and have studied the effect of nitro groups and chlorine atoms in the phenol residue on the rates of neutral and alkaline hydrolysis.
2. The effect of the nitro group in the ortho position of the benzene ring of the benzenesulfonic acid or the phenol on the kinetics of the alkaline hydrolysis of arylsulfonates shows in the first case the presence and in the second case the absence of spatial hindrance. This confirms the acyl-oxygen mechanism of hydrolysis of arylsulfonates.
3. A considerable effect on the rate of neutral hydrolysis is shown by the polarity of the ruptured S-O bond; therefore we submitted to neutral hydrolysis only dinitro-substituted phenyl benzenesulfonates, and also arylsulfonates which contained only one nitro group in the ortho position.
4. Symmetrically distributed methyl groups in benzenesulfonic acid decreased the rate of alkaline hydrolysis and increased the rate of neutral hydrolysis.

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N-SUBSTITUTED AMIDES OF SALICYLIC ACID AND ITS DERIVATIVES

III. ARYLIDES OF 5-AMINOSALICYLIC ACID

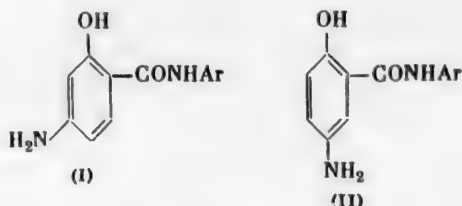
I. S. Ioffe and M. Z. Zal'manovich

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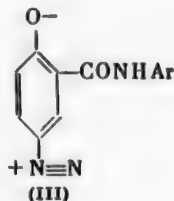
In connection with the wide utilization of 4-aminosalicylic acid (PASA) for the treatment of tuberculosis, various derivatives have been synthesized, including arylides of the general structure (I) [1].



Arylides of 5-aminosalicylic acid of the general structure (II) up to now had not been reported. We have prepared these compounds by reduction of the corresponding nitro compounds, which were described in an earlier communication [2].

All of the arylides of 5-aminosalicylic acid are practically insoluble in water, but they dissolve in alkalis; on acidification of the alkaline solutions with acetic acid the arylides precipitate in the form of fine crystals. On treatment of the arylides with hydrochloric acid, hydrochlorides are formed which have poor solubility in cold water but considerably better in hot water. The purification of the arylides of 5-aminosalicylic acid, was accomplished by crystallization from alcohol, but since the arylides are derivatives of p-aminophenol they readily undergo oxidation and darken on storage. Arylides of 5-aminosalicylic acid are diazotized by sodium nitrite in hydrochloric acid solution. The resulting diazo compounds are practically insoluble in water and in dilute acids. They dissolve without decomposition in mineral acids only upon heating, the diazo compounds being precipitated on cooling these solutions, in the form of white or slightly cream-colored sediment which on filtration and water washing acquires a yellow color.

The mineral acid anion (Cl^- or SO_4^{--}) does not enter into the composition of the diazo compounds thus obtained, just as it is also absent from the composition of diazo compounds obtained from unsubstituted p-aminophenol [3] or from 5-aminosalicylic acid itself [4]. Therefore, such compounds may be considered as inner salts of the structure (III).



While being distinguished by high stability in acidic medium, these diazo compounds are less stable in alkaline medium. In alkaline solutions a gradual decomposition is observed, accompanied by nitrogen evolution, and the solution turns brown, indicating secondary destructive processes. On coupling with β -naphthol in alkaline medium the diazo compounds form red dyes which are freely soluble in alcohol and ether, less soluble in alkali, and insoluble in water.

EXPERIMENTAL*

Preparation of Arylides of 5-Aminosalicylic Acid. A two-gram sample of the arylide of 5-nitrosalicylic acid was dissolved in 25 ml of 10% sodium hydroxide, diluted with 75 ml of water, and heated to 80-90°. Sodium hydrosulfite (2.2-2.5 g) was added gradually to the hot solution with stirring until a light yellow color appeared, and the mixture was filtered rapidly. Fifteen ml of 10% hydrochloric acid was added to the filtrate, and then acetic acid to weakly acid litmus reaction. The precipitate was separated, water-washed, and recrystallized from alcohol (Table 1).

TABLE 1

Arylides of 5-Aminosalicylic Acid (II)

Compound	Melting point	Empirical formula	% N		% Cl	
			calc.	found	calc.	found
Anilide of 5-amino-salicylic acid	175-177°	C ₁₃ H ₁₂ O ₂ N ₂	12.28	12.54, 12.59	—	—
4-Chloranilide of 5-aminosalicylic acid	208-210	C ₁₃ H ₁₁ O ₂ N ₂ Cl	10.66	10.46, 10.65	13.52	13.83
2,5-Dichloranilide of 5-aminosalicylic acid	216-220	C ₁₃ H ₁₀ O ₂ N ₂ Cl ₂	9.42	9.56, 9.56	23.90	24.37
2-Methoxy-4-chloranilide of 5-amino-salicylic acid	205-208	C ₁₄ H ₁₃ O ₃ N ₂ Cl	9.57	9.77, 9.74	12.14	12.80
2-Methoxyanilide of 5-aminosalicylic acid	180-182	C ₁₄ H ₁₄ O ₃ N ₂	10.85	11.19, 11.24	—	—
4-Methoxyanilide of 5-aminosalicylic acid	178-182	C ₁₄ H ₁₄ O ₃ N ₂	10.85	10.69, 10.70	—	—
4-Ethoxyanilide of 5-aminosalicylic acid	143-145	C ₁₅ H ₁₆ O ₃ N ₂	10.29	10.31, 10.25	—	—

Preparation of Diazo Compounds. A 0.05-mole quantity of the arylide of 5-aminosalicylic acid was dissolved in 100 ml of 0.6 N hydrochloric acid, and a solution of 0.05 mole of sodium nitrite in 20 ml of water was added slowly (dropwise) with stirring. A light green precipitate formed gradually; this was filtered off, washed several times with water on the filter, and dried lightly at 30-40°. Then the diazo compound was crystallized from hot hydrochloric acid and dried to constant weight in a thermostat at 90-100° and in a vacuum desiccator over sulfuric acid (Table 2).

TABLE 2

Arylides of 5-Diazosalicylic Acid (III)

Compound	Decomposition temperature	Empirical formula	% N	
			calc.	found
Anilide of 5-diazosalicylic acid	155°	C ₁₃ H ₉ O ₂ N ₃	17.57	17.20, 17.41
4-Chloranilide of 5-diazosalicylic acid	143	C ₁₃ H ₈ O ₂ N ₃ Cl	15.36	15.21, 15.10
2,5-Dichloroanilide of 5-diazosalicylic acid	149	C ₁₃ H ₇ O ₂ N ₃ Cl ₂	13.60	13.34, 13.22
2-Methoxyanilide of 5-diazosalicylic acid	130	C ₁₄ H ₁₁ O ₃ N ₃	15.61	15.30, 15.20

*With the assistance of A. T. D'yakonova.

SUMMARY

The previously unreported arylides of 5-aminosalicylic acid have been prepared: anilide, 2-methoxyanilide, 4-methoxyanilide, 4-chloranilide, 2,5-dichloranilide, 2-methoxy-4-chloranilide, and 4-ethoxyanilide.

The arylides of 5-aminosalicylic acid form practically water-insoluble diazo compounds, which are precipitated in the form of inner salts and are distinguished by unusual stability in neutral and acidic media. They can be recrystallized from hydrochloric acid solutions without decomposition.

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SUBSTITUTED INDAZOLE-3-CARBOXAMIDES AND 3-AMINOMETHYLINDAZOLES

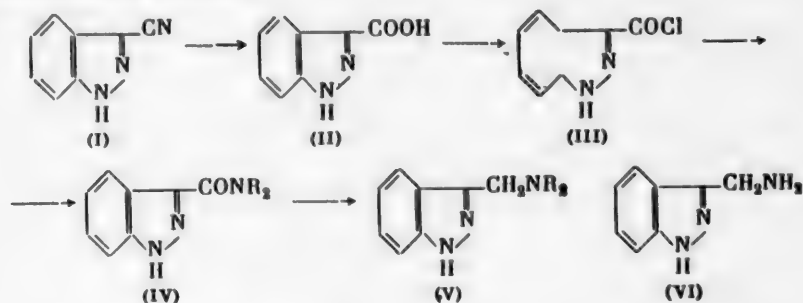
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The synthesis of certain indazole-3-carboxamides and 3-aminomethylindazoles is described in the present communication. The starting material was indazole-3-carbonitrile (I) [1], the final stage of its synthesis (cyclization of o-aminobenzyl cyanide [o-aminophenylacetonitrile]) being carried out according to Pschorr [2]. Saponification of the nitrile (I) by the well-known method of [2] gave indazole-3-carboxylic acid (II); the acid chloride (III) was obtained successfully by treatment of (II) with thionyl chloride in benzene. By the interaction of the acid chloride (III) with ammonia and a number of primary and secondary amines, indazole-3-carboxamides (IV) were obtained. This reaction is most convenient to carry out, heating a mixture of the components in toluene, the amine being taken in excess to combine with the hydrogen chloride evolved. The best yield of the unsubstituted amide was obtained by interaction of the acid chloride (III) with liquid ammonia.



We prepared 3-aminomethylindazoles (V) by reduction of the amides (IV) with lithium aluminum hydride. The most convenient variant of the reduction is the addition of small portions of the dry crystalline amide to an ether solution of the lithium aluminum hydride, taken in threefold excess; it is less convenient to add the amide in the form of an ether suspension. For preparation of 3-aminomethylindazole itself (VI), indazole-3-carbonitrile (I) was reduced with lithium aluminum hydride; the reaction was carried out in ether suspension, using a twofold excess of the reducing agent.

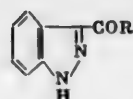
EXPERIMENTAL

Indazole-3-carbonyl Chloride (III). A 5-g quantity of indazole-3-carboxylic acid in 50 ml of anhydrous benzene was heated to boiling for 2-2.5 hr while stirring with 50 ml of thionyl chloride. After vacuum distillation to remove the benzene and excess thionyl chloride, 5.3 g (96%) of a reddish-yellow powder was obtained, insoluble in the majority of organic solvents. Recrystallization from a large quantity of anhydrous benzene gave golden orange-yellow crystals, m.p. 313-317°.

Found %: N 15.97, 15.93. $C_8H_6ON_2Cl$. Calculated %: N 15.56.

Substituted Indazole-3-carboxamides (IV). A suspension of 0.011 mole of indazole-3-carbonyl chloride in 30-40 ml of anhydrous toluene was heated 2-3 hr while stirring with 0.033-0.055 mole of the appropriate amine. The precipitated material was separated and treated 3-4 times with water to remove the amine hydrochloride, and the remaining amide was dried and then recrystallized from alcohol (Table 1).

TABLE 1. Substituted Indazole-3-carboxamides



R	Yield, %	Melting point	Empirical formula	% N	
				found	calc.
NH ₂	95	275—276°	C ₈ H ₇ ON ₃	25.95, 26.37	26.08
N(CH ₃) ₂	70	191—193	C ₁₀ H ₁₁ ON ₃	22.05, 22.23	22.21
N(C ₂ H ₅) ₂	76	180—183	C ₁₂ H ₁₅ ON ₃	19.10, 19.07	19.33
NHC ₆ H ₅	96	203—204	C ₁₄ H ₁₁ ON ₃	17.59, 17.68	17.71
	90	206—208 *	C ₁₃ H ₁₅ ON ₃	18.40, 18.65	18.32
	92	183—184	C ₁₂ H ₁₃ O ₂ N ₃	18.17, 17.98	18.17
NHCH ₂ C ₆ H ₅	81	175—176	C ₁₅ H ₁₃ ON ₃	16.50, 16.30	16.73
	61	177—186	C ₁₈ H ₁₉ O ₂ N ₃	13.71, 13.78	13.58

* Literature data: m.p. 201—203° [3].

Indazole-3-carboxamide. A 1-g quantity of indazole-3-carbonyl chloride was added with stirring to 45 ml of liquid ammonia. After standing for 12 hr at room temperature, 1.1 g of a colorless precipitate was obtained, consisting of a mixture of the amide and ammonium chloride; this material was treated 4 times with water and dried, obtaining 0.85 g (95%) of the amide. Recrystallization from a mixture of alcohol and acetone (3:1) gave colorless fine crystals with m.p. 275—276°.

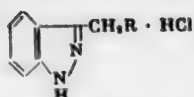
Indazole-3-(N,N-dimethylcarboxamide). A 2-g quantity of indazole-3-carbonyl chloride was added with stirring to 8 g of dimethylamine in 40 ml of cold anhydrous benzene and stirred for 1 hr. After removal of a small amount of precipitate, the benzene filtrate was vacuum-concentrated to 1/3 its original volume; the crystals which were formed were filtered off and treated with water; yield 1.7 g (70%); recrystallization from anhydrous alcohol with carbon gave colorless crystals with m.p. 191—193°. Literature data: m.p. 187—189° [3].

3-Aminomethylindazole. For preparing derivatives of 3-aminomethylindazole, we prepared its hydrochloride by reducing indazole-3-carbonitrile with lithium aluminum hydride. To 5.3 g of lithium aluminum hydride in 100 ml of absolute ether we added with stirring 10 g of indazole-3-carbonitrile in 100 ml of absolute ether; the mixture was heated to boiling for 1 hr. The complex was decomposed first with 30 ml of moist ether, then with 20 ml of water, after which the solution was poured onto a mixture of 60 ml of concentrated hydrochloric acid and 100 g of finely divided ice. To the transparent solution, obtained by heating in a bath, we added 40% NaOH solution; the thick emulsion which was formed was extracted four times with hot ethyl acetate, and after drying the extract over potassium carbonate, the amine was precipitated as the hydrochloride by adding dry hydrogen chloride in ether; yield 12.2 g (95%). Recrystallization from 75% alcohol (with charcoal) gave colorless fine crystals with m.p. 253—255°.

Found %: Cl 19.30, 19.44. C₈H₉N₃·HCl. Calculated %: Cl 19.33.

N-Substituted 3-Aminomethylindazoles. The crystalline amide (0.01 mole) was added in small portions with vigorous stirring to 30–40 ml of an ether solution containing 0.03–0.04 mole of lithium aluminum hydride, and the mixture was heated 1 hr; then the complex was decomposed, adding 20–30 ml of a 20% sodium hydroxide solution; the ether layer was separated from the colorless fine suspension, which was washed 2–3 times more with ether. After drying the ether extract over potassium carbonate, the amine was precipitated in the form of the hydrochloride by adding dry HCl in ether. After recrystallization from a mixture of alcohol and acetone with the addition of ether and rubbing, the pure amine hydrochloride was obtained in the crystalline state (Table 2).

TABLE 2. N-Substituted 3-Aminomethylindazoles



R	Yield %	Melting point	Empirical formula	% N		% Ionic Cl	
				found	calc.	found	calc.
NH ₂	95	253—255°	C ₈ H ₉ N ₃ · HCl	22.53	22.83	19.30, 19.44	19.34
N(CH ₃) ₂	90	84—86	C ₁₀ H ₁₃ N ₃ · HCl	19.80, 19.67	19.85	16.27, 16.44	16.74
N(C ₂ H ₅) ₂	90	195—197	C ₁₂ H ₁₇ N ₃ · HCl	—	—	15.06, 15.12	14.78
NHC ₆ H ₅	93	184—186	C ₁₄ H ₁₃ N ₃ · HCl	15.83, 16.33	16.17	14.48, 14.54	13.65
	95	182—185	C ₁₃ H ₁₇ N ₃ · HCl	16.34, 16.51	16.68	14.22, 14.07	14.08
	91	107—115	C ₁₂ H ₁₅ ON ₃ · HCl	16.43, 16.56	16.60	13.83, 13.75	13.98
NHCH ₂ C ₆ H ₅	85	218—220	C ₁₅ H ₁₅ N ₃ · HCl	15.34, 15.18	15.34	13.21, 13.35	12.96

SUMMARY

1. N-Substituted indazole-3-carboxamides have been prepared by the interaction of indazole-3-carbonyl chloride with ammonia and with primary and secondary amines.

2. N-Substituted 3-aminomethylindazoles have been prepared by reduction of the N-substituted indazole-3-carboxamides with lithium aluminum hydride.

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CYCLOSERINE AND RELATED COMPOUNDS

XI. INFRARED SPECTRA OF ISOXAZOLIDONES-3

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The problem of the structure of isoxazolidone-3 and of its closely related derivatives, a class of compounds which became known only in recent years, is of considerable interest in connection with a study of the physiological activity of the most important representative of this group of compounds—the antibiotic cycloserine (oxamycin) and also in connection with the explanation of the mechanism of its antibiotic action. Moreover, this problem is of interest to organic chemists because it is connected with the study of a new heterocyclic system, which is similar to lactams. The data obtained may be useful in solving the problem of lactim-lactam tautomerism.

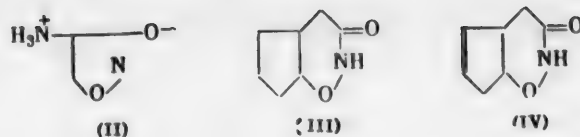
Isoxazolidone-3 (I) and its derivatives, being cyclic O-substituted hydroxamic acids, can a priori exist in the forms (Ia) and (Ib), which may be designated "lactam" and "lactim" or "keto" and "enol" respectively.



It must be kept in mind that in a given case the tautomeric equilibrium will probably be shifted so strongly in one direction that the compound will exist essentially in one form; this has been observed for many analogous systems (for example, α -pyridone [1,2]) and was considered in detail in the well-known paper of A. N. Nesmeyanov and M. I. Kabachnik [3].

Substances included in the isoxazolidone-3 system exhibit several properties which may be explained by the presence of double reactivity. Thus, isoxazolidone-3 dissolves readily in alkalis and forms metallic derivatives with alkali and heavy metals. In comparing the isoxazolidone-3 system with lactams one must take into consideration the fact that the oxygen atom in the ring because of its inductive effect may to a certain extent "acidify" the nitrogen atom of the NH group, thus facilitating the formation of the lactim form (Ib). Information is lacking on the influence of the nature of substituents in isoxazolidone-3 on the structure of the ring.

In the course of a synthetic investigation of cycloserine and of its analogs carried out previously in our laboratory we studied the infrared spectra of isoxazolidone-3 and of those derivatives which were of considerable interest in determining the dependence of the structure of the isoxazolidone ring upon the presence of various substituents in it. At the time of completion of this work, literature data on the infrared spectra of the isoxazolidones-3 or their analogs were limited to a few brief communications. Thus, on the basis of the presence in the infrared spectrum of cycloserine (4-d-aminoisoxazolidone-3) of several absorption bands in the region of $1500-1650\text{ cm}^{-1}$ and $2100-2900\text{ cm}^{-1}$ and absence of absorption corresponding to the hydrogen-bonded NH_2 group, it was concluded that cycloserine is an inner betaine and that it exists in the crystalline state in the form of a bipolar ion (II) [4,5]. On the other hand, in the infrared spectrum of 5,6-trimethyleisoxazinone-3 (III) and of its unsaturated analog (IV) a band was observed with a frequency of about 1667 cm^{-1} , corresponding to an amide carbonyl, and from this it was concluded that compounds (III) and (IV) have a lactam structure [6].



A more detailed study has been made of the infrared spectra of hydroxamic acids, which are related to the isoxazolidones, and of their O-substituted esters [7-9]. All authors have assumed that these compounds have a structure analogous to that of amides. The carbonyl absorption band for these acids is found at 1660-1680 cm^{-1} which is increased somewhat in the case of the corresponding O-substituted esters (1700-1710 cm^{-1}). Similar conclusions were reached in a study of the spectra of deuterated hydroxamic acids of the type RNDOD, in which the presence of intramolecular hydrogen bonds was observed [10]. The latter circumstance may be one reason for the increase in the carbonyl band in the case of the O-esters.

The position of the absorption band corresponding to the C=N vibration is less definite and is subject to major influences from various factors (conjugation [11-13], ring strain, conversion of nitrogen into the positive quadrivalent state [14-15], state of aggregation [16], and others).

In a case very similar to ours where two atoms of oxygen were adjacent to the C=N bond a band having the frequency 1622 cm^{-1} was attributed to the C=N vibration [8]. The presence of a negative charge on one of the oxygens (in the system O-C=N-O) probably favors a further decrease in frequency. Thus, in the case of the silver salt of "albusid" the highest absorption band (for the region 1500-1700 cm^{-1}) is found at 1597 cm^{-1} ; the salts of a number of oxy derivatives of heterogeneous compounds absorb at 1530-1600 cm^{-1} [17].

EXPERIMENTAL

We investigated the infrared spectra of the simplest isoxazolidone and several of its derivatives—cycloserine, its N-acyl and N-methyl derivatives, and also the potassium and silver salts of isoxazolidone-3. All these compounds were prepared by M. Ya. Karpeiski, E. S. Severin, and R. M. Khomutov using methods described in previous papers, and they were analytically pure. The potassium salts of isoxazolidone and its methyl analog were exceptions because their high hygroscopicity resulted in unsatisfactory analyses; however, the method of preparing them excluded the presence of impurities other than water. The infrared spectra were recorded in the region of 1500-3500 cm^{-1} with an IKS-12 spectrometer, the compounds being the form of a paste with vaseline and with a polyfluorinated oil. A sodium chloride prism (calibrated in cm^{-1} [18]) was used.* The accuracy of the measurements in the region of the C=O bond was $\pm 2-3 \text{ cm}^{-1}$, and the region of the valence vibrations of double bonds (1500-1700 cm^{-1}) was used in interpreting the fundamental vibration. The spectra obtained are shown in Figs. 1-3.

DISCUSSION OF RESULTS

The spectrum of isoxazolidone-3 (Fig. 1) contains an intense absorption band at 1670 cm^{-1} , which, on the basis of spectral data on compounds (III), (IV), and hydroxamic acids, which we have already discussed in detail in the introduction, may be attributed to the carbonyl frequency of the amide group-CONH-. It may be concluded therefore that isoxazolidone-3 in the crystalline state exists in the lactam form (Ia). A considerable shifting of the band of the NH group (2944 cm^{-1} from its usual position for secondary amides of 3320-3070 cm^{-1}), as well as its "diffuseness", indicates the presence of strong intermolecular hydrogen bonds. Furthermore, one must consider the possibility of the direct

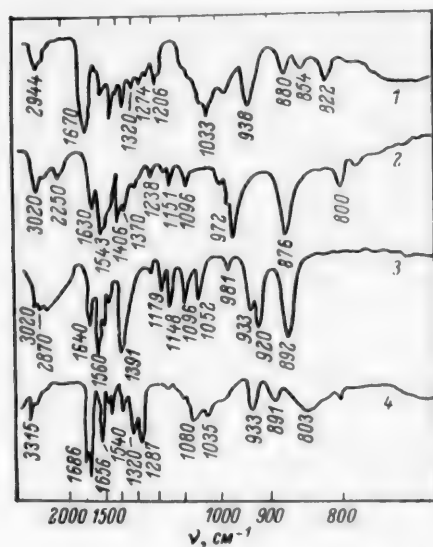
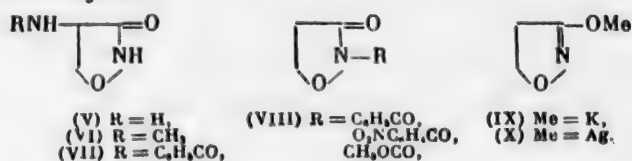


Fig. 1. Infrared spectra of compounds in the crystalline state. 1) Isoxazolidone-3; 2) 4-aminoisoxazolidone-3; 3) 4-methylaminoisoxazolidone-3; 4) 4-N-benzoylaminoisoxazolidone-3.

* Cycloserine, N-methylcycloserine, N-benzoylcycloserine, and isoxazolidone-3 were also studied with a LiF prism.

influence of the oxygen atom in the ring on the strong and stable N-H bond. The comparatively weak bands at 1630 and 1640 cm^{-1} in the region of 1500-1700 cm^{-1} in the spectra of cycloserine (V) and N-methylcycloserine (VI) (Fig.1) may be attributed to $\delta_{\text{as}}\text{NH}_3^+$ and $\delta_{\text{s}}\text{NH}_2^+$.



A very wide absorption band at 1548 cm^{-1} in the spectrum of (V) is probably attributable to vibrations of the groups C=N and $\delta_{\text{as}}\text{NH}_3^+$; the band at 1560 cm^{-1} in the spectrum of (VI) is apparently connected with vibrations of the C=N group only, because the vibrations of $\delta_{\text{as}}\text{NH}_3^+$ in the spectra of N-substituted amino acids were not observed [19]. Much broader bands were observed in the high-frequency region of the spectra, which are also characteristic of α -amino acids [19,20].

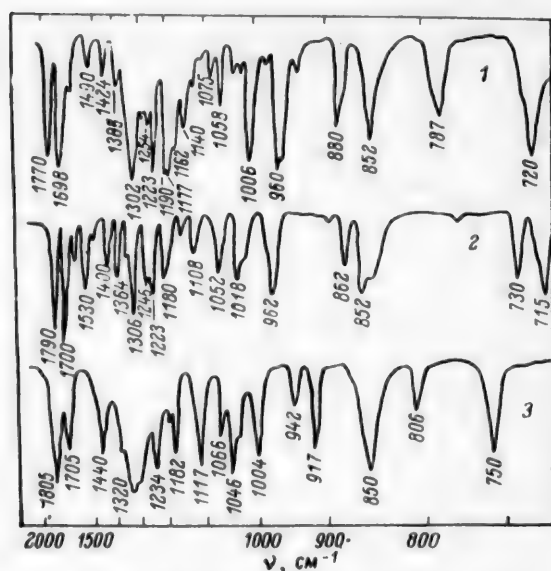


Fig. 2. Infrared spectra of acyl derivatives of isoxazolidone-3 in the crystalline state. 1) N-Benzoyl-isoxazolidone-3; 2) N-p-nitrobenzoylisoxazolidone-3; 3) N-carbomethoxyisoxazolidone-3.

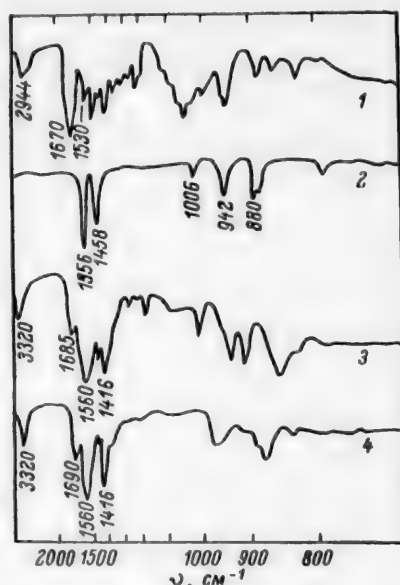


Fig. 3. Infrared spectra of isoxazolidone and its salts in the crystalline state. 1) Isoxazolidone-3; 2) silver salt of isoxazolidone-3; 3) potassium salt of isoxazolidone-3; 4) potassium salt of 4-methylisoxazolidone-3.

The N-benzoylcycloserine (VII) spectrum contains a band at 1656 cm^{-1} which is characteristic of the benzoyl-amino group outside of the ring; this same group accounts for another, less intense band at 1540 cm^{-1} [amide band of (II)]; a band at 1686 cm^{-1} is characteristic of the C=O group of the isoxazolidone ring. It is seen that the frequency of this band is somewhat high by comparison with the frequency of the same group in isoxazolidone-3 itself. This may be explained by an inhibiting action of the benzoylamino group and by a weakening of the hydrogen bonds. This explanation is also supported by a marked decrease in the over-all absorption and the formation of narrower bands in the region of 3300-3000 cm^{-1} in spite of the fact that in (VII) by comparison with (I) there are two NH groups.

Comparison of the data presented leads to the following conclusion. Isoxazolidone-3 exists in the carbonyl (lactam) form (Ia), and the influence of the inductive effect of the oxygen in the ring is insufficient to favor the enol (lactim) form. However, the introduction of a strongly polar nucleophilic group in the α -position to the carbonyl [NH_2 in (V) and CH_3NH in (VI)] has the effect, well known in amino acids, of giving cycloserine and its N-methyl analog the structure of a bipolar ion, which may be considered to be a "limited lactim" structure. This influence of a nucleophilic group on the structure of the ring is well illustrated in the case of the N-benzoyl derivative (VII), where the nucleophilic nature of the amino group is decreased by the introduction of the benzoyl group so that the effect described above is not observed, and the compound (VII) again has the lactam structure.

It is possible that the N-benzoylamino group may also exert some influence on the electronic structure and chemical behavior of this ring; for example, it may decrease the mobility of the NH group and thus hinder the acylation of the heterocyclic ring.

It was shown previously [21] that the same N-acyl derivatives (VIII) are obtained regardless of whether the silver or the potassium salts are used in the acylation of the metal derivatives of isoxazolidone-3, and this is very interesting. The infrared spectra of these N-acyl derivatives are depicted in Fig. 2. There are two characteristic strong bands in the spectra of all three compounds: One band (corresponding to 1770, 1790, and 1805 cm^{-1}) is more intense and apparently is attributable to the carbonyl outside the ring, while the weaker band (corresponding to 1698, 1700, and 1705 cm^{-1}) can be attributed to the carbonyl group in the ring. The anomalously high frequency of the C=O group in these cases may be explained by the strong mutual effect of the two carbonyl groups attached to the same nitrogen atom [8,22] and also by the influence of the oxygen in the ring.

By comparing the spectra of the potassium (IX) and the silver (X) salts of isoxazolidone-3 (Fig. 3) with the spectrum of isoxazolidone-3 itself on the one hand, and with cycloserine on the other, one can see clearly the difference in the first case and the similarity in the second. The presence of an intense band at 1560 cm^{-1} in the spectra of both salts is evidence of the presence of the C=N bond; we showed experimentally that the scarcely noticeable peaks at 1685-1690 cm^{-1} in the spectra of the potassium salts were connected with their hygroscopicity. In other respects the spectra of the K and Ag salts are identical in the region of 1500-1700 cm^{-1} , which indicates that they have a completely similar structure containing a C=N double bond and therefore belonging to the oxygen-metal type. Thus, isoxazolidone-3 behaves like several other heterocyclic systems, for example α -pyridone and other analogous compounds, the salts of which were shown conclusively by Yu. N. Sheinker [2,17] to have the oxygen-metal type of structure. In our case the nitrogen atom, in spite of the additional effect of the oxygen atom in the ring, is less electronegative than the oxygen of the carbonyl group, which therefore makes possible the formation of oxygen-metal derivatives.

In conclusion it should be noted that in the case of isoxazolidone-3 itself and also of its analogs the reason for the formation of two series of derivatives should not be sought in the tautomerism of these compounds. It is much more probably connected with the possibility that a transfer of an active center is involved when these compounds react.

The authors are grateful to Yu. N. Sheinker for several valuable suggestions in the discussion of our results.

SUMMARY

1. The infrared spectra of isoxazolidone-3, its K and Ag salts, N-acyl derivatives, and also cycloserine, N-methylcycloserine and N-benzoylcycloserine were investigated.

2. The data obtained indicate that isoxazolidone-3 and N-benzoylcycloserine in the crystalline state have a keto (lactam) structure, while cycloserine and its N-methyl derivative form a bipolar ion type of structure, which shows the determining influence of the amino group in position 4 of the ring on the structure of this heterocyclic system.

3. It was shown that the metal derivatives of isoxazolidone-3 have an oxygen-metal type of structure regardless of the nature of the metal.

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DERIVATIVES OF 4-PHOSPHINYLSEMICARBAZIDE

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Phosphoniscyanatidic dichloride and diethers show strongly marked properties of isocyanates and readily undergo addition at the $-NCO$ group with alcohols, phenols [1], amines [2], and phosphorous diesters [3]. It was of interest to examine whether hydrazine and its derivatives would add to phosphoniscyanatidic dichloride and diesters.

Experiments have shown that aryl-, benzoyl-, and also 1,1-dimethylhydrazines easily add to phosphoniscyanatidic dichloride, forming 1-aryl-, 1-benzoyl-, and 1,1-dimethyl-4-(dichlorophosphinyl)semicarbazides.



1-Aryl- and 1-benzoyl-4-(dichlorophosphinyl)semicarbazides (I) are colorless, crystalline compounds (Table 1, Nos. 1 and 3-6), quite easily hydrolyzed by the moisture in the air. Compounds obtained from p-nitro- and 2,4-dinitrophenylhydrazine are yellow. The structure of compounds (I) as 1,4-disubstituted semicarbazides (cf. [4]) is strictly proved by the fact that during hydrolysis with water they are converted to 1-monosubstituted semicarbazides (Table 2), thus excluding the structure of 2,4-disubstituted semicarbazides



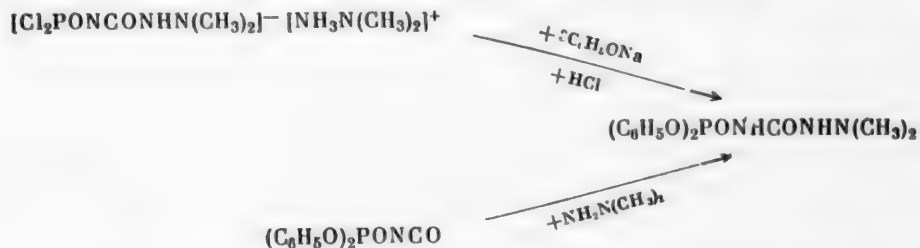
Unsubstituted hydrazine and phosphoniscyanatidic dichloride form a crystalline dihydrazine salt of 1,6-bis(dichlorophosphinyl)biurea.



Phosphoniscyanatidic dichloride and 2 moles of 1,1-dimethylhydrazine form the 1,1-dimethylhydrazine salt of 1,1-dimethyl-4-(dichlorophosphinyl)semicarbazide (Table 1, No. 2):



This salt forms the sodium salt of 1,1-dimethyl-4-(diphenoxyphosphinyl)semicarbazide with 3 moles of sodium phenolate. The latter on acidification yields free 1,1-dimethyl-4-(diphenoxyphosphinyl)semicarbazide, identical with the substance obtained from diphenyl phosphoniscyanatide and 1,1-dimethylhydrazine.



On hydrolysis of 4-(dichlorophosphinyl)-1,1-dimethylsemicarbazide (Table 1, No. 2) 1,1-dimethylhydrazine was formed; it was isolated and identified as 3,3-dimethyldithiocarbamic acid.

TABLE 1. 4-Dichlorophosphinylsemicarbazides

Compound No.	R	R'	Yield, %	Melting point	Appearance	Found %		Empirical formula	Calculated %		Solubility*			
						N	Cl		N	Cl	ether	benzene	acetone	di-oxane
1	H	C ₆ H ₅	86	160—163° (dec.)	Small prisms	15.56, 15.41	26.54, 26.74	C ₇ H ₈ O ₂ N ₃ PCl ₂	15.67	26.49	—	—	—	—
2	CH ₃	CH ₃	99 **	110—113 (dec.)*	The same	24.38, 24.52	25.96, 26.06	C ₈ H ₁₀ O ₂ N ₃ PCl ₂ **	25.00	25.36	—	—	—	—
3	H	p-CH ₃ C ₆ H ₄	79	114—117 (dec.)	Prisms	—	24.97, 24.95	C ₉ H ₁₀ O ₂ N ₃ PCl ₂	—	25.18	—	—	—	—
4	H	p-NO ₂ C ₆ H ₄	98	188—190 (dec.)	Needles	17.43, 17.52	22.20, 20.14	C ₇ H ₇ O ₄ N ₄ PCl ₂	17.89	22.68	—	—	—	—
5	H	2,4-(NO ₂) ₂ C ₆ H ₃	99	175—177 (dec.)	The same	—	19.22, 19.48	C ₇ H ₆ O ₆ N ₃ PCl ₂	—	19.99	—	—	—	—
6	H	C ₆ H ₅ CO	70	126—128 (dec.)	Small prisms	—	23.36, 23.67	C ₁₃ H ₁₂ O ₃ N ₃ PCl ₂	—	24.00	—	—	—	—

* Symbols: + very soluble at 20°; + very soluble at boiling point; —slightly soluble at boiling point, = insoluble at boiling point. All compounds (1) are insoluble at boiling point in petroleum ether and CCl₄.

** As 1,1-dimethylhydrazine salt. Solubility: water +, alcohol +.

TABLE 2. Semicarbazides $\text{NH}_2\text{CONHNHR}$

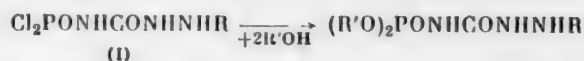
R	Yield, %	M.p.
C_6H_5	60	166—168° [5]
p- $\text{CH}_3\text{C}_6\text{H}_4$	73	192—193 [6]
p- $\text{NO}_2\text{C}_6\text{H}_4$	71	208—209 [7]
2,4-(NO_2) $_2\text{C}_6\text{H}_3$	75	212—215 (dec.)
$\text{C}_6\text{H}_5\text{CO}$	70	218—219 [8]

* 1-(2,4-Dinitrophenyl)semicarbazide is not described in the literature. The needles are organic; soluble on heating in water, alcohol, acetone, and dioxane. Found %: N 28.24, 28.56. $\text{C}_7\text{H}_7\text{O}_6\text{N}_5$. Calculated %: N 29.05.

Dimethyl and diphenyl phosphonoisocyanatidates, and also phosphonoisocyanatidic dichloride, very easily add aryl hydrazines, benzoyl hydrazine, and 1,1-dimethylhydrazine, forming 1-aryl-, 1-benzoyl-, and 1,1-dimethyl-4-[dimethoxy(or diphenoxy)phosphinyl]semicarbazides (II), which are colorless, crystalline compounds (Table 3) quite readily soluble in the usual organic solvents.



The nitro derivatives (Table 3, Nos. 7-10) are light yellow. Compounds (II) have characteristics of weak acids: They are soluble in aqueous alkaline solutions and are titrated as monobasic acids with phenolphthalein. Their structure is proved by the fact that they do not react with aldehydes [the structure $(\text{RO})_2\text{PONHCONR}'\text{NH}_2$ is excluded] and also by the fact that they have been obtained by the action of alcohol on compounds (I).



With dimethyl and diethyl phosphonoisocyanatidates, unsubstituted hydrazine forms 1,6-bisdimethoxy(and diphenoxy)phosphinylbiureas



which are colorless, crystalline substances. They have the characteristics of weak acids and are soluble in aqueous alkaline solutions, forming very soluble salts.

EXPERIMENTAL

4-(Dichlorophosphinyl)semicarbazides (I) (Table 1). Compounds 1-3. To a solution, cooled to 2-3°, of 0.1 mole of phosphonoisocyanatidic dichloride in 50 ml of anhydrous ether was added dropwise a solution of 0.1 mole of arylhydrazine or 0.2 mole of 1,1-dimethylhydrazine in 50 ml of ether. The reaction product precipitated out. After two hours the precipitate was sucked off in a current of dry air, washed with ether (2 times, 10 ml), and dried in a vacuum desiccator. The freshly prepared products were analyzed.

Compounds 4-6. Finely ground substituted hydrazine (0.1 mole) was added to a solution of 0.1 mole of phosphonoisocyanatidic dichloride in 70 ml of benzene. Slight heating was observed. In the case of benzoylhydrazine a change in the character of the precipitate was noticeable: The shiny benzoylhydrazine crystals disappeared, and a fine powder of 1-benzoyl-4-(dichlorophosphinyl)semicarbazide appeared. The reaction went to completion in a day. In the case of p-nitrophenyl- and 2,4-dinitrophenylhydrazines, the mixture was boiled about two hours with a reflux condenser. The completion of the reaction could be judged by the disappearance of the dark-red color of the initial arylhydrazines. The precipitated products were sucked off in a current of dry air, washed with benzene (2 times, 10 ml), and dried in a vacuum desiccator.

Hydrolysis of 4-(dichlorophosphinyl)semicarbazides (I). Compound No. 1 (Table 1) (0.02 mole) was added to 20 ml of 10% NaHCO_3 solution and the mixture heated for 5 minutes at 60-70°. The substance passed into solution, and simultaneously 1-phenylsemicarbazide precipitated. After cooling, it was sucked off, washed with cold water (2 times, 5 ml), and recrystallized. The identification was by a mixed melting point.

A mixture of 0.2 mole of compounds 3-6 (Table 1) and 30 ml of water was boiled for ten minutes; the solution was filtered while hot and left standing overnight. The precipitated 1-substituted semicarbazides (Table 2) were sucked off, washed with water (2 times, 5 ml), and recrystallized. The identification was by melting point.

For the isolation and identification of 1,1-dimethylhydrazine, which is the hydrolysis product of compound No. 2 (Table 1), the solution was boiled down in vacuum to a small volume, neutralized with 50% potassium hydroxide, and a small excess added. 1,1-Dimethylhydrazine, which separated as an oil, was isolated and an equivalent quantity of carbon disulfide added to it. An exothermic reaction took place, and a crystalline 1,1-dimethylhydrazine salt of 3,3-dimethyldithiocarbamic acid was formed, which upon treatment with glacial acetic acid was converted to colorless, crystalline 3,3-dimethyldithiocarbamic acid. It was sucked off, washed with acetic acid and ether, and dried in air. The identification was by a mixed melting point.

TABLE 3. Phosphinylisemicarbazides (RO)₂PONHCONHR* (II)

No.	R	R'	R''	Yield* (%)	M.p.	Appearance; crystallization solvent	Found		Calculated % N**	Solubility***					
							% N	equiv.		water	alcohol	ether	benzene	acetone	dioxane
1	CH ₃	H	C ₆ H ₅	93 (32)	166-167 ^b	Needles; water	16.32, 16.94	0.98, 0.99	16.22	+	+	+	+	+	+
2	C ₆ H ₅	H	C ₆ H ₅	85	157-163	Needles; alcohol	10.75, 10.94	1.03, 0.93	10.96	+	+	+	+	+	+
3	CH ₃	H	p-CH ₃ C ₆ H ₄	76 (46)	147-148	The same	15.47, 15.61	0.95, 0.97	15.38	+	+	+	+	+	+
4	C ₆ H ₅	H	p-CH ₃ C ₆ H ₄	93	176-177	Thin needles; alcohol	10.21, 10.39	0.95, 0.98	10.38	+	+	+	+	+	+
5	CH ₃	H	C ₆ H ₅ CO	91	149-150	Needles; water or dioxane	14.28, 14.45	0.94, 0.93	14.63	+	+	+	+	+	+
6	C ₆ H ₅	H	C ₆ H ₅ CO	93	187-181	Needles; alcohol	10.22, 10.12	0.95, 0.95	10.22	+	+	+	+	+	+
7	CH ₃	H	p-NO ₂ C ₆ H ₄	87 (70)	164-165 (dec.)	The same	18.21, 18.31	—	18.42	+	+	+	+	+	+
8	C ₆ H ₅	H	p-NO ₂ C ₆ H ₄	80	211-213 (dec.)	Needles; nitro-benzene	13.19, 13.31	—	13.08	—	—	—	—	—	—
9	CH ₃	H	2,4-(NO ₂) ₂ C ₆ H ₃	99 (63)	193-200 (dec.)	Needles; acetone or alcohol	20.13, 20.16	—	20.06	+	+	+	+	+	+
10	C ₆ H ₅	H	2,4-(NO ₂) ₂ C ₆ H ₃	85	202-203 (dec.)	Needles; nitro-benzene	14.65, 14.75	—	14.80	—	—	—	—	—	—
11	CH ₃	CH ₃	CH ₃	87	109-110	Prisms; benzene or chloroform	19.69, 19.57	—	19.91	+	+	+	+	+	+
12	C ₆ H ₅	CH ₃	CH ₃	90	123-130	Small plates; water	12.65, 12.78	—	12.54	+	+	+	+	+	+

* The yields according to procedure B are given in parentheses.

** Calculated equiv. 1.00.

*** All substances are insoluble in boiling petroleum ether; for solubility symbols see Table 1.

Dihydrazine salt of 1,6-bisdichlorophosphinylbiurea. A solution of 0.04 mole of phosphonoisocyanatidic dichloride in 40 ml of absolute ether was added with stirring to an emulsion of 0.06 mole of hydrazine in 50 ml of absolute ether. The precipitate came down immediately; it was sucked off, washed with ether (2 times, 10 ml), and dried in a vacuum desiccator. Yield 91%, m.p. 213-215° (decomposition), small prisms. The salt is very soluble in water; insoluble in the usual organic solvents.

Found %: N 26.45, 26.60; Cl 34.41, 34.57. $C_2H_{12}O_4N_4P_2Cl_4$. Calculated %: N 26.92; Cl 34.13.

Phosphinylsemicarbazides (II) (Table 3). A. From phosphonoisocyanatidates. Compounds 1-4, 11-12. To a solution, cooled to 2-3°, of 0.1 mole of dimethyl or diphenyl phosphonoisocyanatidate in 50 ml of absolute ether was added dropwise a solution of 0.1 mole of arylhydrazine or 1,1-dimethylhydrazine. The mixture was left standing overnight. The precipitate was sucked off, washed with ether (2 times, 10 ml), dried, and crystallized.

Compounds 5-8. Dioxane was used as a solvent in the same quantities as ether. Thus the precipitates often did not appear until 1-2 hours after the components were mixed. Anhydrous ether (30-40 ml) was added to the mixture for precipitation of that portion of substance which remained in the dioxane solution. The precipitate was sucked off, washed with a mixture of dioxane and ether (1 : 2; 3 times, 5 ml) and with ether (2 times, 10 ml) and recrystallized.

Compounds 9,10. To a solution of 0.1 mole of dimethyl or diphenyl phosphonoisocyanatidate in 70 ml of dioxane, 0.1 mole of finely ground 2,4-dinitrophenylhydrazine was added. The completion of reaction was judged by the change in color from bright red to light yellow. The compound was sucked off on the following day, washed with dioxane (2 times, 10 ml), dried, and recrystallized.

B. From 4-dichlorophosphinylsemicarbazides. Compounds 1,3,7,9. To 50 ml of cooled anhydrous methyl alcohol 0.05 mole of the corresponding 4-dichlorophosphinylsemicarbazine (I) was added. The latter quickly dissolved, and compounds 7 and 9 began to precipitate as beautiful thin needles. They were sucked off, dried, and crystallized. Compounds 1 and 3 are soluble in methyl alcohol, and therefore to isolate them methyl alcohol was boiled off in vacuum and the residue crystallized from water. The substances did not give a melting point depression in a mixture with compounds 1,3,7, and 9 prepared according to method A.

Compound 12. Compound 2 (0.01 mole) (Table 1) was added to a suspension of 0.03 mole of sodium phenolate in 50 ml of benzene, and the mixture was boiled for four hours with a reflux condenser. After cooling, sodium chloride was sucked off and washed with benzene (2 times, 10 ml). To precipitate the sodium salt of 1,1-dimethyl-4-(diphenoxyphosphinyl)semicarbazide, 20 ml of anhydrous ether was added to the benzene solution. The salt was sucked off, dissolved in the minimum quantity of water, and the solution acidified with hydrochloric acid to Congo red. 1,1-Dimethyl-4-(diphenoxyphosphinyl)semicarbazide separated as an oil which gradually crystallized on standing. After twofold recrystallization from water the compound did not give a melting point depression in a mixture with compound 12 prepared according to method A.

1,6-Bisdimethoxyphosphinylbiurea, $(CH_3O)_2PONHCONHNHCONHPO(OCH_3)_2$. To an emulsion, cooled to 2°, of 0.025 mole of hydrazine in 40 ml of anhydrous dioxane was added dropwise 0.05 mole of dimethyl phosphonoisocyanatidate in 100 ml of benzene. The precipitate came down immediately; it was sucked off after three hours, washed with 10 ml of benzene, and dried. After recrystallization from water, yield 96%, m.p. 183-184° (small prisms). The substance is soluble in water and alcohol; insoluble in all other organic solvents.

Found %: N 16.59, 16.61. $C_8H_{16}O_8N_4P_2$. Calculated %: N 16.74.

1,6-Bisdiphenoxyphosphinylbiurea, $(C_6H_5O)_2PONHCONHNHCONHPO(OC_6H_5)_2$ was prepared similarly to the above. For purification it was recrystallized twice from 50% alcohol; small prisms, yield 85%, m.p. 188-190°. The substance is soluble in alcohol, acetone, dioxane; insoluble in water, ether, benzene, CCl_4 , and ligroin.

Found %: N 9.44, 9.59. $C_{26}H_{24}O_8N_4P_2$. Calculated %: N 9.62.

SUMMARY

1. Phosphonoisocyanatidic dichloride and diesters undergo addition at the isocyanate group with hydrazine, benzoylhydrazine and arylhydrazines, forming the corresponding derivatives of 1,6-bisphosphinylbiurea: 1,1-dimethyl-4-phosphinylsemicarbazide, 1-benzoyl-4-phosphinylsemicarbazide, and 1-aryl-4-phosphinylsemicarbazides.

2. The structure of 1-benzoyl- and 1-aryl-4-(dichlorophosphinyl)semicarbazides as 1,4-disubstituted semicarbazides is proved by the fact that on hydrolysis they yield 1-benzoyl- and 1-arylsemicarbazides.

3. The structure of 1-benzoyl- and 1-aryl-4-[dimethoxy(or diphenoxy)phosphinyl]semicarbazides is proved by their chemical properties and the synthesis of 1-aryl-4-(dimethoxyphosphinyl)semicarbazides by the action of methanol on 1-aryl-4-(dichlorophosphinyl)semicarbazides.

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SULFONATION AND SULFONIC ACIDS OF ACIDOPHOBIC COMPOUNDS

XXIX. GEOMETRICAL ISOMERISM OF UNSATURATED SULFONIC ACIDS.

SYNTHESIS OF UNSATURATED SULFONES

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In the preceding communication [1] it was shown that ultraviolet irradiation of ω -styrenesulfonamide (m.p. 143°) leads to formation of a lower-melting isomer (m.p. 96°) which is evidently the *cis* isomer.



This is supported by the character of the vibration spectra (infrared and Raman) of the two forms of the amide. The amide with m.p. 143° was synthesized from the sulfonic acid chloride obtained by sulfonation of styrene with pyridinesulfotrioxide.

In the present work we showed by chemical methods that the sulfonic acid of styrene and its derivatives (amide and chloride) are *trans* isomers.

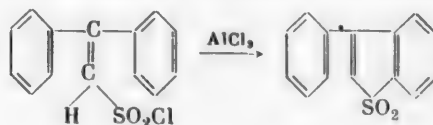
Even a comparison of the reactivities of the two forms of the amide permits the conclusion that the higher melting amide has a *trans*-structure. Its solution in methanol decolorizes bromine water very much more slowly than a solution of the same concentration of the lower melting amide (21 and 7 min respectively).

Configuration and stereochemistry can be determined by formation of a cyclic system and by transformation of investigated stereoisomers into compounds of known configuration. In this work we made use of both methods.

If the chloride of ω -styrenesulfonic acid had *cis* configuration then treatment with aluminum chloride should result in cyclization with formation of thionaphthene-S-dioxide



It was found that heating of styrenesulfochloride with aluminum chloride does not give the sulfone; the compound breaks down, with liberation of sulfur dioxide. It follows that the original styrenesulfochloride has the *trans* configuration. Such a process of intramolecular cyclization is possible, however, in principle and can be realized with facility. We demonstrated this in the case of 1,1-diphenylethylene-2-sulfochloride. We treated the latter with aluminum chloride in a medium of carbon disulfide or nitrobenzene and obtained 3-phenylthionaphthene-S-dioxide.



The literature mentions two stereoisomeric sulfones with m.p. 121 and 77°. They were prepared by a rather complicated route [2]



The high-melting isomer evidently has *trans* structure. By acting on styrenesulfochloride with toluene in presence of aluminum chloride, we obtained *p*-tolylstyrylsulfone with m.p. 121°, thus confirming the *trans* structure of the styrenesulfonic acid that we had synthesized.

We used ω -styrenesulfochloride for synthesis of other unsaturated sulfones. Reaction of styrenesulfochloride with dimethyl- and diethylaniline in presence of 2 moles of aluminum chloride in a solution of the appropriate tertiary amine gave the unsaturated aminosulfones in good yields.

EXPERIMENTAL

3-Phenylthionaphthene-S-dioxide. A mixture of 0.018 mole of 1,1-diphenylethylene-2-sulfochloride and 0.023 mole of aluminum chloride was heated in 50 ml of carbon disulfide on a water bath until evolution of hydrogen chloride ceased. The mass was decomposed with water and acidified with hydrochloric acid. Chloroform was added until the product of cyclization had been completely extracted. The solution was washed with water. Distillation of the solvents left 3.1 g of cyclic sulfone with m.p. 161° (from alcohol).

Found %: C 69.86, 69.90; H 4.24, 4.38. $C_{14}H_{10}O_2S$. Calculated %: C 69.42; H 4.16.

Nitration of 3-phenylthionaphthene-S-dioxide. A solution of 0.26 g of nitric acid (d 1.41) in concentrated sulfuric acid was added dropwise to a solution of 1 g of 3-phenylthionaphthene-S-dioxide in concentrated sulfuric acid. The reaction was exothermic and the mixture darkened. The reaction mass was allowed to stand for 30 min and then poured into ice water; the nitrosulfone was washed with water. Yield 1.1 g; m.p. 180-181° (decomp.).

Found %: N 4.91, 4.98. $C_{14}H_9O_4NS$. Calculated %: N 4.88.

***p*-Tolylstyrylsulfone.** To 0.01 mole of sublimed aluminum chloride in 25 ml of toluene was slowly added a solution of 0.01 mole of styrenesulfochloride in 25 ml of toluene with stirring. The aluminum chloride went into solution; hydrogen chloride at once started to come off and the solution darkened. The mass was stirred for 5 hr and then decomposed with ice water. The organic layer was collected and the toluene taken off in vacuo. The residual oil crystallized rapidly. The sulfone was filtered, washed with a little toluene, and recrystallized from methyl alcohol. Yield 32%; m.p. 121°.

Found %: C 69.96, 70.12; H 5.74, 5.62. $C_{15}H_{14}O_2S$. Calculated %: C 69.79; H 5.46.

***p*-Dimethylaminophenylstyrylsulfone.** Into 0.02 mole of ω -styrenesulfochloride in 30 ml of freshly distilled dimethylaniline was stirred 0.04 mole of aluminum chloride in portions. The reaction was exothermic and the color of the solution became dark violet. When no more heat was released, the mixture was allowed to stand for 4 hr at room temperature, then decomposed with ice water and treated with concentrated alkali. The organic layer was collected and distilled with steam. The residue in the flask was dissolved in acetone and the sulfone brought down with water; yield 5.2 g. Recrystallization from alcohol and then from acetone gave the sulfone in the form of lustrous, small, white plates with a blue tinge; m.p. 181-181.5° (the melt was green).

Found %: C 66.73, 66.58; H 5.73, 5.72. $C_{15}H_{17}O_2NS$. Calculated %: C 66.87; H 5.96.

***p*-Diethylaminophenylstyrylsulfone** was similarly prepared. The black resinous substance remaining after steam distillation was dissolved in acetone, the solution filtered, and the sulfone brought down with water. There was obtained 4.5 g of sulfone in the form of light-brown, small needles with m.p. 139-140° (from methanol).

Found %: C 68.39, 68.38; H 6.28, 6.31. $C_{18}H_{21}O_2NS$. Calculated %: C 68.54; H 6.71.

SUMMARY

ω -Styrenesulfonic acid formed by sulfonation of styrene with pyridinesulfotrioxide is shown to have *trans* configuration.

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THIOINDIGOID DYES

VI. ETHOXY- AND ETHOXYNITRO-SUBSTITUTED THIOINDIGOS

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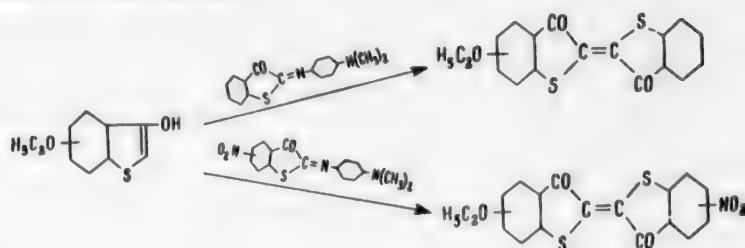
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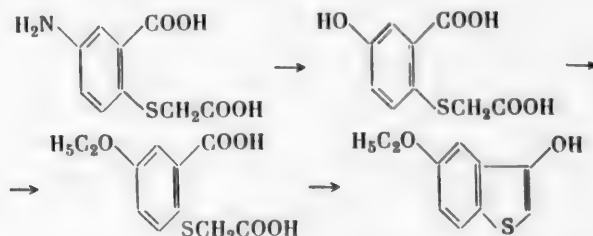
In continuation of earlier research [1] on the color of unsymmetrical thioindigoid dyes, we now examine the problem of the color of ethoxy- and nitroethoxyindigos in which the nitro and ethoxy groups are in different benzene rings.

Some monosubstituted thioindigos have been described in the literature [2], but the influence of one substituent on the color of thioindigo was not studied. In one of our preceding papers [1] we examined the color change of thioindigo on introduction of one nitro group into the molecule of a dye. However, derivatives of thioindigo containing substituents of different characters in different benzene rings are generally unknown.

We synthesized 5-ethoxy- and 6-ethoxythioindigo as well as four isomeric ethoxynitrothioindigos with substituents in the 5- and 6-positions. Dyes were prepared by condensation of 5-ethoxy- and 6-ethoxy-3-hydroxythionaphthene with thionaphthenequinone-2-(p-dimethylamino)-anil (in the case of synthesis of monoethoxy derivatives) and with 5-nitro- and 6-nitrothionaphthenequinone-2-(p-dimethylamino)-anil, previously described by us [1] (in the case of synthesis of ethoxynitro derivatives).



The previously unknown 5-ethoxy-3-hydroxythionaphthene was prepared from S-(2-carboxy-4-aminophenyl)-thioglycolic acid.



Oxidation of 5-ethoxy-3-hydroxythionaphthene gave 5,5'-diethoxythioindigo.

We could not obtain 5-ethoxy-3-hydroxythionaphthene by cyclization of S-(4-ethoxyphenyl)-thioglycolyl chloride in presence of aluminum chloride, whereas 3-hydroxythionaphthene and a series of its derivatives can be obtained under these conditions from the corresponding derivatives of S-phenylthioglycolic acid (see for example [2]).

TABLE 1

Prep. no.	Name of dye	λ_{\max}	$\epsilon_{\max} \cdot 10^{-4}$
1	5,5'-Diethoxythioindigo	588	1.1
2	6,6'-Diethoxythioindigo	515	1.0
3	5-Ethoxythioindigo	561	1.1
4	6-Ethoxythioindigo	531	1.0
5	5-Ethoxy-5'-nitrothioindigo	562	1.0
6	5-Ethoxy-6'-nitrothioindigo	578	1.1
7	6-Ethoxy-5'-nitrothioindigo	527	1.1
8	6-Ethoxy-6'-nitrothioindigo	549	1.4

The absorption spectra of benzene solutions of all of the prepared dyes were determined. We see from Table 1 that the only unsymmetrical dyes whose absorption maximum is situated more deeply in the short-wave region than the maximum of thioindigo (545 m μ) are 6-ethoxythioindigo and 6-ethoxy-5'-nitrothioindigo. On comparison with the absorption maxima of the corresponding symmetrical dyes (we previously reported the absorption maxima of the dinitro derivative [3]) it was found that the maximum for 5-ethoxythioindigo is shifted towards the short-wave region relative to the arithmetic mean of the absorption maxima of the corresponding symmetrical dyes (566.5 m μ), while the absorption maxima of 6-ethoxythioindigo and 5-ethoxy-6'-nitrothioindigo deviate very inappreciably from the calculated values (530 and 577.5 m μ respectively). The remaining three dyes have absorption maxima at wavelengths longer than those calculated (for 5-ethoxy-6'-nitrothioindigo 550.5 m μ , for 6-ethoxy-5'-nitrothioindigo 514 m μ , and for 6-ethoxy-6'-nitrothioindigo 541 m μ).

The absorption spectrum of some of the dyes contains an additional absorption maximum of shorter wavelength corresponding to the *cis* form [4]: for 6,6'-diethoxythioindigo 478 m μ , $\epsilon_{\max} 0.85 \cdot 10^4$; for 6-ethoxythioindigo 489 m μ , $\epsilon_{\max} 0.85 \cdot 10^4$; and for 6-ethoxy-5'-nitrothioindigo 469 m μ , $\epsilon_{\max} 1.0 \cdot 10^4$.

EXPERIMENTAL

S-(2-Carboxy-4-aminophenyl)-thioglycolic acid. To a suspension of 26.0 g of S-(2-carboxy-4-nitrophenyl)-thioglycolic acid in 250 ml of water were added 165 g of ferrous sulfate and 150 ml of 25% ammonia. The mixture was refluxed with stirring for 1.5 hr and cooled; another 50 ml of ammonia was added. After filtration, the filtrate was evaporated to half of its bulk and acidified with acetic acid to bring down S-(2-carboxy-4-aminophenyl)-thioglycolic acid; yield 15.9 g (70%), m.p. 205.0-206.0. Crystallization from water gave colorless crystals with m.p. 226.0-227.0° (decomp.); the literature [5] gives m.p. 227° (decomp.).

S-(2-Carboxy-4-hydroxyphenyl)-thioglycolic acid. Diazotization of 11.5 g of S-(2-carboxy-4-aminophenyl)-thioglycolic acid in 100 ml of water and 15 ml of sulfuric acid (d 1.83) was effected with 13 ml of 4 M sodium nitrite solution at 15-20°. A further 30 ml of sulfuric acid was added and the mass heated for 6 hr on a boiling water bath. Resin was removed from the hot solution with active carbon, and the product was extracted from the cooled filtrate with ether. Evaporation of the ether left 8.6 g of substance (75.5%) with m.p. 163-165° (decomp.). Crystallization from water gave colorless crystals with m.p. 197.0-199.0° (decomp.).

Found %: C 47.23, 47.30; H 3.22, 3.58; S 14.26, 14.28. $C_9H_6O_5S$. Calculated %: C 47.35; H 3.53; S 14.05.

S-(2-Carboxy-4-ethoxyphenyl)thioglycolic acid. A mixture of 4.56 g of S-(2-carboxy-4-hydroxyphenyl)-thioglycolic acid, 30 ml of water, 5 g of sodium hydroxide, and 7 g of ethyl p-toluenesulfonate was vigorously stirred for 8 hr at 70-80°. The mass was cooled, filtered, and acidified to give 2.88 g (56.5%) of substance with m.p. 181-184°. Crystallization from water gave colorless needles with m.p. 186.0-187.0°. The literature [6] reports m.p. 186-187°.

5-Ethoxy-3-hydroxythionaphthene. A mixture of 2.40 g of S-(2-carboxy-4-ethoxyphenyl)-thioglycolic acid, 10 ml of acetic anhydride, and 1.2 g of anhydrous sodium acetate was boiled for half an hour and the acetic anhydride evaporated in vacuo. The residue was boiled for half an hour in sodium hydroxide solution and then acidified. The 5-ethoxy-3-hydroxythionaphthene was distilled off with steam. Yield 1.10 g (60.5%) with m.p. 93.0-95.0°. Crystallization from n-hexane gave yellowish needles with m.p. 104.0-105.0°.

Found %: C 62.20, 61.80; H 5.07, 5.18; S 16.29, 16.33. $C_{10}H_{10}O_2S$. Calculated %: C 61.80; H 5.19; S 16.50.

A mixture of 0.4 g of 5-ethoxy-3-hydroxythionaphthene, 1.2 ml of acetic anhydride, and 0.1 g of anhydrous sodium acetate was boiled for 10 min. Addition of water brought down 5-ethoxy-3-acetoxythionaphthene as colorless needles with m.p. 51.5-52.0° (from alcohol).

Found %: C 61.00, 61.20; H 5.60, 4.87; S 13.71, 13.51. $C_{11}H_{12}O_3S$. Calculated %: C 60.98; H 5.12; S 13.57.

5-Ethoxythionaphthenequinone-2-(p-dimethylamino)-anil. To 0.39 g of 5-ethoxy-3-hydroxythionaphthene and 0.32 g of p-nitrosodimethylaniline in 10 ml of water was added sodium hydroxide until the reaction was alkaline. The mass was stirred at room temperature for 20 hr, then heated to 70°, and 40 ml of water was added. The product was filtered and washed with hot water. Yield 0.59 g (90.5%), m.p. 174.0-176.0°. Crystallization from chlorobenzene gave red crystals with a green tinge, m.p. 178.9-179.0°.

Found %: N 8.72, 8.76; S 9.70, 9.61. $C_{18}H_{18}O_2N_2S$. Calculated %: N 8.52, S 9.82.

5,5'-Diethoxythioindigo. To a solution of 0.58 g of 5-ethoxy-3-hydroxythionaphthene and 0.25 g of sodium hydroxide in 15 ml of water was added 3 ml of 2 M sodium tetrasulfide solution and the mixture stirred for an hour at 80-90°. The dye was filtered and washed with water and alcohol. Yield of product (blue powder) 0.53 g (92%). Crystallization from nitrobenzene gave fine, blue-violet needles with m.p. 294-297°. The solution of the dye in concentrated sulfuric acid had a yellowish-green color.

Found %: C 62.86, 62.68; H 4.51, 4.59; S 16.78, 16.84. $C_{20}H_{20}O_4S_2$. Calculated %: C 62.48; H 4.20; S 16.69.

Cyclization of S-(4-ethoxyphenyl)-thioglycolic acid. To a solution of 2.12 g of S-(4-ethoxyphenyl)-thioglycolic acid [7] in 40 ml of chlorobenzene was added 1.5 g of phosphorus trichloride. The mixture was heated to 80° and held at that temperature for an hour. It was then cooled to 20°; 1.8 g of aluminum chloride was added and the mixture stirred for 2 hr. 5-Ethoxy-3-hydroxythionaphthene was not detected in the residue after the chlorobenzene had been removed by steam distillation. Cyclization likewise did not take place at 0 and 40°. Replacement of phosphorus trichloride by thionyl chloride at the stage of preparation of the acid chloride likewise did not give satisfactory cyclization.

6-Ethoxy-3-hydroxythionaphthene was obtained by the method of [8]; acetylation as described above gave 6-ethoxy-3-acetoxythionaphthene in the form of colorless crystals with m.p. 59.0-60.0° (from alcohol).

Found %: C 61.27, 60.94; H 5.26, 5.19; S 13.76, 13.56. $C_{12}H_{12}O_3S$. Calculated %: C 60.98; H 5.12; S 13.57.

6,6'-Diethoxythioindigo [8] was prepared by a procedure similar to that for the 5,5' isomer. An orange powder, soluble in concentrated sulfuric acid with a violet color.

TABLE 2

Substituent in the thioindigo molecule	Empirical formula	Yield, %	Color of crystals	Color of solution in H_2SO_4	Melting point	Found, %	
						N	S
5-OC ₂ H ₅	$C_{18}H_{12}O_3S_2$ *	88	Violet	Green	235-238°	—	18.70
6-OC ₂ H ₅	$C_{18}H_{12}O_3S_2$ *	94	Orange-red	Red-violet	262-285	—	18.74
							18.79
							18.63
5-OC ₂ H ₅ , 5'-NO ₂	$C_{18}H_{11}O_5NS_2$ **	95	Blue-violet	Blue	285-290 (decomp)	3.73,	16.55,
5-OC ₂ H ₅ , 6'-NO ₂	$C_{18}H_{11}O_5NS_2$ **	85	Dark blue	Blue	335-340 (decomp)	3.69	16.35
6-OC ₂ H ₅ , 5'-NO ₂	$C_{18}H_{11}O_5NS_2$ **	91	Brownish	Blue	345-350 (decomp)	3.77,	16.58
6-OC ₂ H ₅ , 6'-NO ₂	$C_{18}H_{11}O_5NS_2$ **	88	Brownish	Green	350-355 (decomp)	3.84	16.73
						3.62,	16.82
						3.71	16.63
						3.48,	16.39
						3.54	16.39

* Calculated %: S 18.85.

** Calculated %: N 3.64; S 16.69.

Unsymmetrical dyes. To 12 ml of acetic acid was added 0.39 g of 5- or 6-ethoxy-3-hydroxythionaphthene, 0.2 ml of piperidine, and (in the case of synthesis of the monoethoxy derivative) 0.57 g of thlonaphthenequinone-(p-dimethylamino)-anil or (in the case of synthesis of the ethoxynitro derivative) 0.66 g of 5- or 6-nitrothlonaphthenequinone-2-(p-dimethylamino)-anil. The mixture was refluxed and stirred for 2 hr, cooled, and filtered. The product was washed with hot alcohol and crystallized from nitrobenzene. Yields of dyes, some of their properties, and analytical data are set forth in Table 2.

SUMMARY

Two ethoxy-substituted and four ethoxynitro-substituted thioindigos were synthesized, and their absorption spectra in benzene were measured.

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REACTIONS OF ALUMINUM ISOPROPOXIDE WITH SOME ORGANOPHOSPHORUS COMPOUNDS

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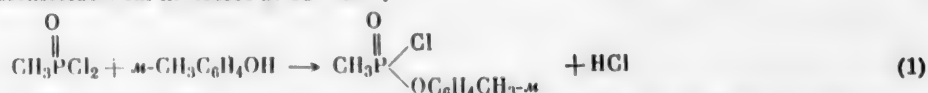
pp. 224-228, January, 1961

Original article submitted February 20, 1960

Investigators have devoted a great deal of attention in recent years to the synthesis of polymers in which the main chains of the molecules are constructed of aluminum and oxygen, while the framing groups are alkoxy [1] and aroxy [2] radicals, groups susceptible to keto-enol tautomerism [3,4], and acyl groups [5]. Polymers whose framing groups are trialkylsiloxy groups have also been investigated [6,7]. According to the literature data, none of the aforementioned groups is joined to an aluminum atom by a hydrolytically stable bond, and under the action of moisture such polymers tend to form branched or three-dimensional structures. An attempt has been made [8] to synthesize polyalumoxanes in which the framing groups are methylbutoxyphosphinic acid residues with the objective of obtaining a stable phosphorus-oxygen aluminum bond.

The present work is devoted to the preparation of methyl-m-cresoxyphosphinoxy(diisopropoxy)aluminum and dimethylphosphinoxy(diisopropoxy)aluminum to serve as starting substances for synthesis of polymers containing inorganic chains of molecules.

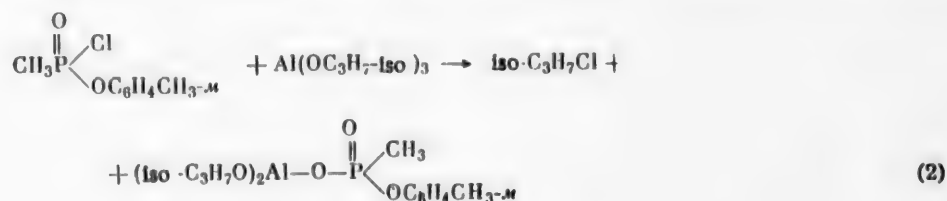
One of the starting organophosphorus compounds—methyl-m-cresoxyphosphinic chloride—was prepared by reaction of methylphosphinic dichloride with m-cresol at 120-140°:



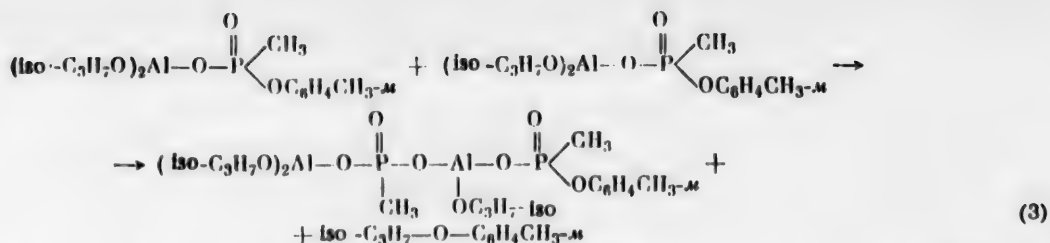
A reaction product, apart from methyl-m-cresoxyphosphinic chloride, was di-m-cresyl methylphosphinate, formed in considerable quantity.

The effect of variation of the molar ratio of methylphosphinic dichloride and m-cresol was studied. Increase in the excess of methylphosphinic dichloride increases the yield of methyl-m-cresoxyphosphinic chloride and slightly lowers the yield of di-m-cresyl methylphosphinate. In all cases, however, the yield of ester is 30-50% by weight of the yield of methyl-m-cresoxyphosphinic chloride.

We can expect the reaction of methyl-m-cresoxyphosphinic chloride with aluminum isopropoxide to follow the course:

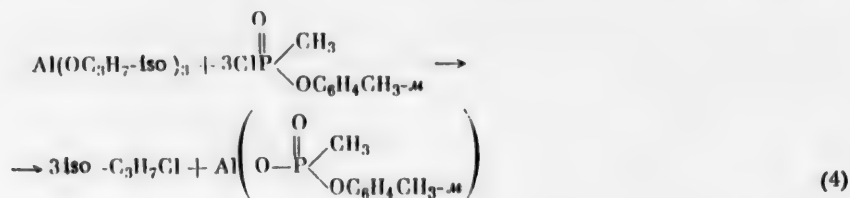


Experiments showed that, in accordance with equation (2), isopropyl chloride was formed during the process. At the same time, however, isopropyl m-cresyl ether was formed. This pointed to secondary reactions associated with reaction of the isopropoxy group of aluminum isopropoxide with the m-cresoxy group of methyl-m-cresoxyphosphinic chloride. We were able to show that this reaction takes place at a temperature above 120°. Isopropyl m-cresyl ether could not be isolated from the reaction mixture when the reaction was run at below 100°. In our opinion, isopropyl m-cresyl ether is formed by the following mechanism:



The results show that this reaction is not limited to formation of dimer but can also proceed at 140-200° with formation of more complex compounds. Considerable difficulty was encountered in attempts to isolate pure substances because of the lack of a selective solvent.

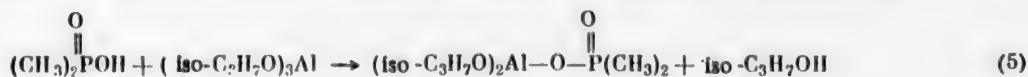
For confirmation of the proposed reaction mechanism, we synthesized tris(methyl-m-cresoxyphosphinoxy)aluminum by the route:



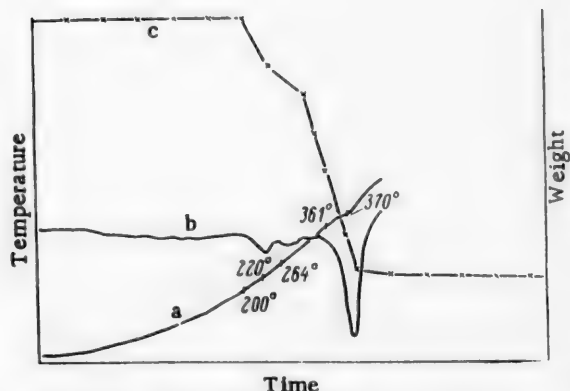
The reaction was performed at 90-100° to avoid the risk of detachment of the cresoxy group. Under these conditions tris(methyl-m-cresoxyphosphinoxy)aluminum was obtained in 59% yield and isopropyl chloride in 67% yield. These data confirm our ideas about the course of the process.

Thermochemical investigation* of tris(methyl-m-cresoxyphosphinoxy)aluminum showed that the sample begins to lose weight gradually at 200°. Maximum loss of weight is observed at 370°, and thereafter the weight remains nearly constant (see figure). The weight loss is 53.7%, corresponding to complete loss of the organic part of the molecule (the inorganic content is 47.7%).

Reaction of dimethylphosphonic acid with aluminum isopropoxide goes according to the equation



Equation (5) is confirmed by the nearly quantitative liberation of isopropyl alcohol (99%).



Thermogram and curve of weight change of tris(methyl-m-cresoxyphosphinoxy)aluminum: a) temperature, b) differential temperature curve, c) weight of sample.

* The authors thank G. B. Ravich and I. F. Manucharova for carrying out the thermographic analysis.

Judging by the elemental analysis the product distilling from the reaction mixture at 164° (2 mm) is dimethylphosphinoxy(diisopropoxy)aluminum rendered impure by secondary products. The molecular weight of the isolated product is nearly three times higher than the value calculated for dimethylphosphinoxy(diisopropoxy)aluminum. This points to association in solution. The product is a colorless, glassy substance, readily soluble in aromatic solvents, alcohols, carbon tetrachloride, ether, and ligroins.

EXPERIMENTAL

Methyl-m-cresoxyphosphinic dichloride. Methylphosphinic dichloride (31.65 g) was put into a round-bottomed flask fitted with stirrer, reflux condenser and calcium chloride tube, thermometer, and dropping funnel. To the fused acid chloride, heated to 120-130°, was added 21.36 g of m-cresol dropwise in the course of 3 hr. The reaction mass was

then heated for 2.5 hr at 120-130° and for another 2.5 hr at 130-140°. Hydrogen chloride was evolved (89.5% of the calculated quantity). The following fractions were collected on fractional distillation of the mixture: 1st, 55-120° (16 mm), 9.5 g; 2nd, 116-124° (2 mm), 19.01 g; 3rd, 124-170° (2 mm), 0.68 g; 4th, 170-187° (2 mm), 9.67 g. The first fraction corresponded to methylphosphinic dichloride, the 2nd to methyl-m-cresoxyphosphinic chloride. Yield of second product 47.2%. Methyl-m-cresoxyphosphinic chloride was collected at 118° (2 mm) after two distillations.

d_4^{20} 1.238, n_D^{20} 1.5212, MR_D 50.54; calc. 50.24.

Found %: C 46.56; H 4.97; Cl 17.16; P 15.06. $C_8H_{10}O_2PCl$. Calculated %: C 46.96; H 4.93; Cl 17.33; P 15.14.

Two distillations of the 4th fraction gave di-m-cresyl methylphosphinate with b.p. 177° (2 mm).

d_4^{20} 1.155, n_D^{20} 1.5445, MR_D 75.76; calc. 75.58.

Found %: C 65.27; H 6.17; P 11.20. $C_{16}H_{17}O_3P$. Calculated %: C 65.21; H 6.20; P 11.22.

Other ratios of starting components were also taken for synthesis of methyl-m-cresoxyphosphinic chloride:

1) 99.91 g of methylphosphinic dichloride and 54.21 g of m-cresol; the yield of methyl-m-cresoxyphosphinic chloride was 59.3%; 2) 133 g of acid chloride and 54 g of m-cresol; the yield of methyl-m-cresoxyphosphinic chloride in this case was 61.5%.

Methyl-m-cresoxyphosphinic (diisopropoxy) aluminum. Aluminum isopropoxide and methyl-m-cresoxyphosphinic chloride were reacted in a round-bottomed flask equipped with stirrer, dropping funnel, sloping condenser, and a receiver with calcium chloride tube. The receiver was cooled by dry ice. Methyl-m-cresoxyphosphinoxy chloride was stirred dropwise at a bath temperature of 125-136° in the course of 1.5 hr into a melt of 35.34 g of aluminum isopropoxide. The bath temperature was then raised to 130-150° and the reaction mixture heated for another 2.5 hr. The reaction mass was washed on the filter with cold ligroine. The residual product on the filter was completely insoluble in aromatic solvents, alcohols, ether, and acetone. The product had the following composition:

Found %: C 41.15; H 6.25; Cl 5.22; ash 45.46.

After distillation of the ligroine, the filtrate was distilled to give 3.36 g of isopropyl m-cresyl ether. Redistillation of the latter gave a product with b.p. 82° (16 mm).

d_4^{20} 0.9327, n_D^{20} 1.4969, MR_D 47.12; calc. 46.81.

Found %: C 79.41; H 9.27; ash 0.34. M 138.8. $C_{10}H_{14}O$. Calculated %: C 79.95; H 9.39. M 150.2.

A violent reaction occurred when fractional distillation of the residue of filtrate was attempted. An infusible white powder (13.12 g) was formed.

Tris(methyl-m-cresoxyphosphinoxy)aluminum. The reaction was carried out in a Claisen flask equipped with a condenser and a receiver (with calcium chloride tube) cooled by dry ice. A mixture of 21.68 g of methyl-m-cresoxyphosphinic chloride and 7.21 g of aluminum isopropoxide was heated in the flask. Isopropyl chloride was slowly evolved. The reaction went very violently at a bath temperature of 102°. There was obtained 6.5 ml of isopropyl chloride. The latter was collected at 34.5° on redistillation.

d_4^{20} 0.8585, n_D^{20} 1.3764, MR_D 21.02; calc. 20.86.

The product formed in the flask was dissolved in xylene. Treatment of the solution with ligroins resulted in precipitation of 12.17 g of amorphous, infusible powder.

Found %: C 47.27; H 5.22; Cl 1.49; Al 5.91; P 15.93. $C_{24}H_{30}O_9P_3Al$. Calculated %: C 49.49; H 5.19; Al 4.63; P 15.96.

Dimethylphosphinic acid was prepared by oxidation of bis(dimethylphosphine) with hydrogen peroxide [9]. Bis(dimethylphosphine) was obtained by anomalous organomagnesium synthesis from phosphorus thiochloride [10].

Dimethylphosphinoxy (diisopropoxy) aluminum. A mixture of 34.53 g of aluminum isopropoxide and 150 g of toluene was placed in a round-bottomed flask equipped with stirrer and reflux condenser (with calcium chloride tube). To the resulting solution was added 15.90 g of dimethylphosphinic acid. The mixture was heated to the boil and stirred at that temperature for 6 hr. Isopropyl alcohol (10.07 g) was distilled from the mass. The quantity of alcohol was determined from the content of hydroxyl groups. The residual mixture was transferred to a Claisen flask; the toluene was distilled off and the residue heated at a bath temperature of 200° for an hour. Fractional distillation gave two fractions: 1st, 160-163° (2 mm), 10.35 g; 2nd, 164° (2 mm), 16.30 g. The 2nd fraction corresponded to dimethylphosphinoxy (diisopropoxy) aluminum.

SUMMARY

1. Reactions of aluminum isopropoxide with methyl-m-cresoxyphosphinic chloride and dimethylphosphinic acid were investigated.

2. The following new compounds were synthesized: methyl-m-cresoxyphosphinic acid, di-m-cresyl methylphosphinate, tris(methyl-m-cresoxyphosphinoxy)aluminum, and dimethylphosphinoxy (diisopropoxy)aluminum.

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SYNTHESIS OF POLY(PHENOXYMETHYLPHOSPHINOXY)ALUMOXANES

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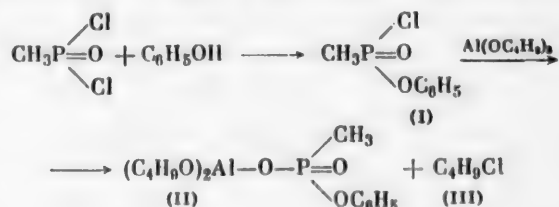
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Aluminum, titanium, boron, tin, arsenic, phosphorus, and other elements have recently been used in addition to silicon in the synthesis of chain polymers. Work has been carried out on the synthesis of polymers whose main chain was built up from metal-oxygen-metal groupings while the framing groups were trialkylsiloxy groups [1,2], alkoxyl and weakly acidic groups, as well as groups susceptible to keto-enol tautomerism [3], and others.

We have studied the reactions of some phosphoroaluminorganic compounds and the possibility of their transformation into polymers with a main alumoxane chain.

The synthesis of phosphoroaluminorganic compounds was effected by esterification of methylphosphinic chloride with phenol followed by reaction of the resulting methylphenoxyphosphinic chloride with aluminum n-butoxide:



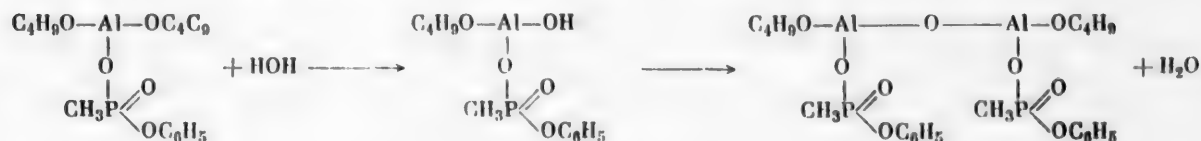
Methylphenoxyphosphinic chloride (I) has not previously been described. It was isolated in pure form by fractional distillation of the reaction products (yield 26.2%). This low yield is due to partial replacement of the second chlorine by the phenoxy group with formation of the compound $\text{CH}_3\text{PO}(\text{OC}_6\text{H}_5)_2$. Reaction of methylphosphinic chloride with phenol gave in addition a considerable quantity of still residue, probably consisting of a mixture of products of condensation of the organophosphorus compounds present.

Butyl chloride was isolated in 58% yield. The yield was lowered by large losses during vacuum distillation of solvent from the product. Reaction at 80-90° gave phenoxymethylphosphinoxidibutoxyaluminum (II). Reaction at higher temperatures gave compounds insoluble in the usual organic solvents.

Phenoxymethylphosphinoxidibutoxyaluminum is a solid substance, soluble in butyl alcohol and cellosolves (at room temperature), and in benzene, toluene, and xylene (with heating).

The butoxyl groups of the phenoxy compound appear to undergo hydrolysis under the action of water. Attempts were therefore made to synthesize, by hydrolytic treatment of the compound, polymers with a main chain of aluminum and oxygen atoms framed by phenoxymethylphosphinoxy groups.

Experiments showed that hydrolysis of phenoxymethylphosphinoxidibutoxyaluminum is accompanied by fairly rapid rise in viscosity of the product of hydrolysis. The reaction mechanism may be represented as follows:



Hydrolysis was performed in a medium of butyl alcohol containing various proportions of water. Samples were taken off at intervals during the hydrolysis for determination of the relative viscosity of a 5% solution in butyl alcohol. The rise in viscosity was found to depend on the quantity of water taken for hydrolysis. The greater the quantity of water, the higher the viscosity of the products of hydrolysis. At the commencement of hydrolysis the viscosity increases very quickly. It later comes to a standstill, probably due to attainment of equilibrium of the hydrolysis reaction and of the condensation reaction. This conclusion is confirmed by the observation of the sharp rise in viscosity of products isolated from the solution after they had been redissolved.

The products of hydrolysis isolated from solution were solid substances soluble in butyl alcohol. Hard, brittle films were formed after application of solutions of the polymers to solid surfaces and evaporation of the solvent.

Investigation of the thermomechanical properties of the products of hydrolysis (Figs. 1 and 2) showed that an increase in the quantity of water taken for hydrolysis of phenoxymethylphosphinobutoxyaluminum had no appreciable influence on the flow temperature of the polymer; however an increase in the quantity of water taken for hydrolysis slightly lowers the interval between the temperatures of vitrification and flow.

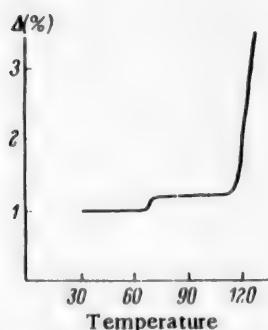


Fig. 1. Thermomechanical curve of product of hydrolysis of phenoxymethylphosphinobutoxyaluminum with 1.5 moles of water.

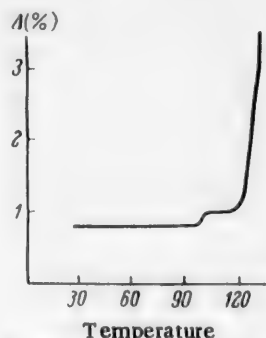


Fig. 2. Thermomechanical curve of product of hydrolysis of phenoxymethylphosphinobutoxyaluminum with 3.0 moles of water.

EXPERIMENTAL

Preparation of methylphenoxyphosphinic chloride. A mixture of 211.7 g of methylphosphinic chloride and 133.6 g of phenol was placed in a flask equipped with thermometer, mechanical stirrer, and reflux condenser topped by a calcium chloride tube. The mixture was stirred for 24 hr at 125–130° until hydrogen chloride no longer came off. Arrival at this stage was established by periodic weighing of the reaction products. The resulting mixture was twice fractionated from a Claisen flask. The following fractions were obtained: 1st, boiling up to 72° (1.5 mm), 11.2 g; 2nd, 72–80° (1.5 mm), 76.8 g; the residue amounted to 192.3 g. The second fraction corresponded to methylphenoxyphosphinic chloride. Yield 26.2 g.

B.p. 72–80° (1.5 mm), MR_D 45.69; calc. 45.79.

Found %: C 45.75, 45.41; H 4.89, 4.96; P 17.70, 18.04; Cl 18.03, 17.60. M 204. $C_7H_9O_2PCl$. Calculated %: C 44.14; H 4.23; P 16.25; Cl 18.61; M 191.

Preparation of phenoxymethylphosphinobutoxyaluminum. A flask like that in the preceding experiment was charged with 18.45 g of aluminum n-butoxide and 56 g of xylene. The heated mixture was stirred until the aluminum n-butoxide had dissolved completely. The mixture was cooled and through a dropping funnel was added 14.28 g of methylphenoxyphosphinic chloride diluted with 15 g of xylene. The contents of the flask were heated at 50° for 3 hr and at 80° for 6 hr. The xylene and butyl chloride were distilled off in vacuo at an oil bath temperature not exceeding 80°. Chlorine was detected in the product. The latter was therefore redissolved in xylene and the xylene again taken off in vacuo at a bath temperature of 80°. In this way a product free of chlorine was obtained. Yield of phenoxymethylphosphinobutoxyaluminum 25.3 g (98.7%).

Found %: P 8.66, 8.75; Al 8.70, 8.52. $C_{15}H_{25}O_5PAl$. Calculated %: P 8.97; Al 7.84.

Hydrolysis of phenoxymethylphosphinoxidibutoxyaluminum. Known quantities of phenoxymethylphosphinoxidibutoxyaluminum and n-butyl alcohol were put into a flask equipped with thermometer, mechanical stirrer, and reflux condenser. The mixture was heated until the phenoxy compound had completely dissolved. The relative viscosity of the resulting solution was determined after dilution with n-butyl alcohol to 5% concentration. The solution was thereupon heated to 80° and additions were made of the calculated quantity of water, diluted with n-butyl alcohol, and of pure n-butyl alcohol so as to give a 10% solution of phenoxymethylphosphinoxidibutoxyaluminum. The mixture was stirred for 3-3.5 hr at 75-80°. At specific time intervals samples of the product of hydrolysis were withdrawn and diluted with n-butyl alcohol to give a 5% solution whose relative viscosity was then measured. The products of hydrolysis were isolated from solution by evaporation in vacuo.

SUMMARY

1. Methylphenoxyphosphinic chloride and phenoxymethylphosphinoxidibutoxyaluminum were synthesized for the first time.
2. The hydrolysis of phenoxymethylphosphinoxidibutoxyaluminum was studied, and it was shown that hydrolysis is accompanied by polycondensation with formation of poly(phenoxymethylphosphinoxy)alumoxanes.

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SYNTHESIS OF HALOESTERS OF ORTHOTITANIC ACID

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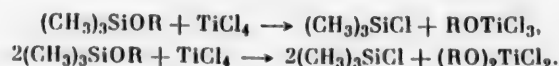
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Original article submitted February 15, 1960

Existing methods of synthesis of haloesters of orthotitanic acid are based on three types of reactions: a) action of alcohols or phenols on titanium tetrachloride [1]; b) replacement of one or more RO groups in $Ti(OH)_4$ or in $Ti(OR)_nX_{4-n}$ by halogen atoms with the aid of acid halides [2], hydrogen halides [3], pyridine hydrochloride [4,5], or free halogens [5]; c) replacement of some RO groups in $Ti(OR)_nX_{4-n}$ by others in a transesterification process [6].

Reference is made in the literature [7] to the possibility of cleavage of the Si-O-Si bond by titanium tetrachloride [7].

The above data prompted us to attempt the synthesis of alkoxytitanium chlorides from trialkylalkoxysilanes and titanium tetrachloride. It was found that trimethylalkoxysilanes react violently with titanium tetrachloride according to the equations:



We failed to replace the alkoxy group by more than two atoms of chlorine from $TiCl_4$ when using a 1:3 molar ratio of $TiCl_4$ to $(CH_3)_3SiOR$ in spite of prolonged heating of the reactants.

The properties of the resulting alkoxytitanium chlorides are set forth in the table. Our method may be of preparative interest. Experiments were run under conditions excluding access of atmospheric moisture to the thoroughly dried reactants.

Compound	Boiling point (pressure in mm)	Melting point	% Ti		% Cl	
			calc.	found	calc.	found
Ethoxytitanium trichloride	185°	—	24.03	23.81, 23.90	53.37	52.86
Diethoxytitanium dichloride	—	40—50°	22.93	23.82	33.96	33.09, 33.11
Butoxytitanium trichloride	65—80 (0.5—1)	50—60	21.07	21.58	46.79	46.15
Isopropoxytitanium trichloride	—	77—78	—	—	49.88	49.60

EXPERIMENTAL

1. Ethoxytitanium trichloride. Dropwise addition of 11.8 g (0.1 mole) of trimethylethoxysilane was slowly made from a dropping funnel to 19 g (0.1 mole) of titanium tetrachloride in the flask of a distillation apparatus. The reaction was strongly exothermic. Fractional distillation at atmospheric pressure gave a 56–57° fraction (9.64 g, yield 88.8%) and a 185° fraction (11.6 g, yield 58.4%). The first fraction contained 32.09% of titratable chlorine and was identified as trimethylchlorosilane. The 185° fraction (light-yellow crystals) was ethoxytitanium trichloride.

Found %: Ti 23.81, 23.90; Cl 52.86. $C_2H_5OTiCl_3$. Calculated %: Ti 24.03, Cl 53.37.

2. Diethoxytitanium dichloride. The flask of a distillation apparatus was charged with 9.5 g (0.05 mole) of titanium tetrachloride, and 11.8 g (0.1 mole) of trimethylethoxysilane was slowly added dropwise from a dropping funnel. The reaction was strongly exothermic. The reaction mass was then subjected to fractional distillation at a bath temperature of up to 100° at normal pressure. There was distilled off 8.4 g (77.5%) of trimethylchlorosilane with b.p. 56°. Chloride ion content 32.8%.

The residue in the flask crystallized after cooling. The product was diethoxytitanium dichloride with m.p. 40-50° (from benzene). Yield nearly quantitative.

Found %: Ti 23.82; Cl 33.09, 33.11. $(C_2H_5O)_2TiCl_2$. Calculated %: Ti 22.93; Cl 33.96.

3. Butoxytitanium trichloride. The flask of a distillation apparatus was charged with 19 g (0.1 mole) of titanium tetrachloride, and 14.6 g (0.1 mole) of trimethylbutoxysilane was slowly added from a dropping funnel. The reaction was strongly exothermic. The mass was subjected to fractional distillation and at normal pressure 8.53 g (79%) of trimethylchlorosilane came over at 56°. Titratable chlorine content 33.1%. Vacuum distillation then gave 15.4 g (67.6%) of butoxytitanium trichloride with b.p. 65-80° (0.5-1 mm). Light-yellow crystals with m.p. 50-60° (in sealed capillary).

Found %: Ti 21.58; Cl 46.15. $C_4H_9OTiCl_3$. Calculated %: Ti 21.07; Cl 46.79.

4. Isopropoxytitanium trichloride. The flask of a distillation apparatus was charged with 19 g (0.1 mole) of titanium tetrachloride, and 13.2 g (0.1 mole) of trimethylisopropoxysilane was slowly introduced dropwise from a dropping funnel. The mixture was strongly exothermic. The trimethylchlorosilane was taken off in vacuo. The residue in the flask was washed with ligroine and analyzed without being recrystallized. M.p. 77-78°. Yield nearly theoretical.

Found %: Cl 49.60. Iso- $C_3H_7OTiCl_3$. Calculated %: Cl 49.88.

SUMMARY

Trialkylalkoxysilanes react with titanium tetrachloride with formation of trialkylchlorosilane and alkoxytitanium chlorides. Ethoxytitanium trichloride, diethoxytitanium dichloride, butoxytitanium trichloride, and isopropoxytitanium trichloride were synthesized.

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SOME DIKETODICARBOXYLIC SILICOORGANIC ACIDS

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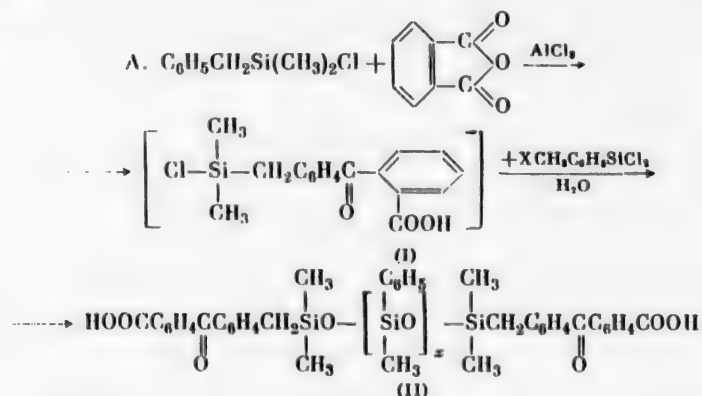
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It was shown earlier that acylation of silicoorganic compounds containing a benzyl group at the silicon atom leads to synthesis of silicoorganic diketodicarboxylic acids [1].

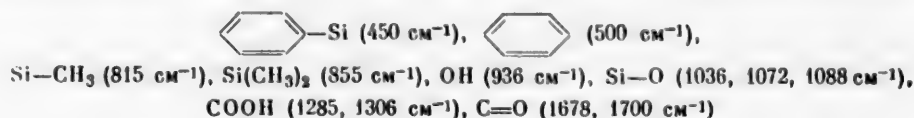
In continuation of our work on the acylation of silicoorganic compounds, we carried out this reaction with the aim of preparing diketodicarboxylic acids with the aid of phthalic and maleic anhydrides as acylating agents and with simultaneous introduction of methylphenylsiloxane groups into the diketodicarboxylic acid molecule.

Synthesis of dibasic silicoorganic diketo acids with the help of phthalic anhydride as acylating agent was realized by the following scheme:

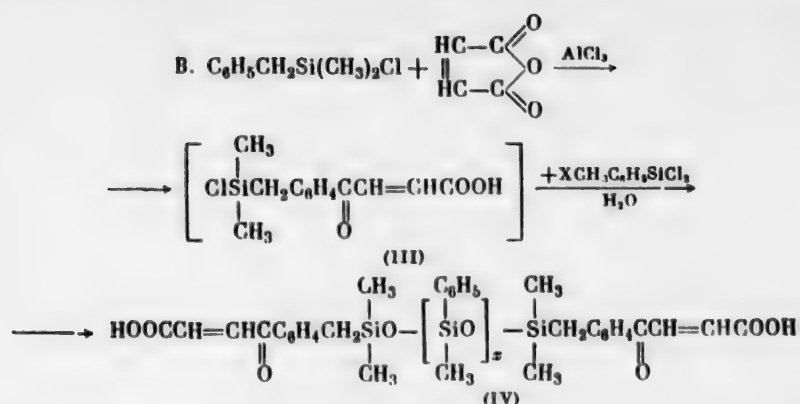


Diketodicarboxylic silicoorganic acids containing a number of methylphenylsiloxane groups equal to X (X = 1, 2, 3, 4, 5, 10) were obtained by altering the ratio of the acylation product (I) to methylphenyldichlorosilane during hydrolysis by reaction A. These acids have good solubility in alcohol, acetone, ether, benzene, toluene, carbon tetrachloride, and chloroform. The diketodicarboxylic silicoorganic acids, both unpurified and when purified via their salts, are viscous, transparent liquids that do not crystallize at room temperature even after prolonged standing. The viscosity of the acids depends on the number of methylphenylsiloxane groups in the molecule, and it increases with the number of such groups. The composition and structure of the acids were confirmed by analytical data and by the results of infrared examination.

Fig. 1 contains the infrared absorption spectrum for the diketodicarboxylic acid in which X (the number of methylphenylsiloxane groups) is ten. The figure gives the vibration frequencies corresponding to the following groups:



Using maleic anhydride as the acylating agent, diketodicarboxylic silicoorganic acids were prepared by the following reaction:



Cohydrolysis of product (III) with methylphenyldichlorosilane gave silicoorganic diketodicarboxylic acids in which the number (X) of methylphenylsiloxane groups in the molecule was 1,2,3,4,5,10. All of the acids are viscous liquids that do not crystallize at room temperature. They have good solubility in alcohol, ether, benzene, xylene, toluene, and chloroform. The elemental composition and the infrared spectroscopic data are consistent with the above structure.

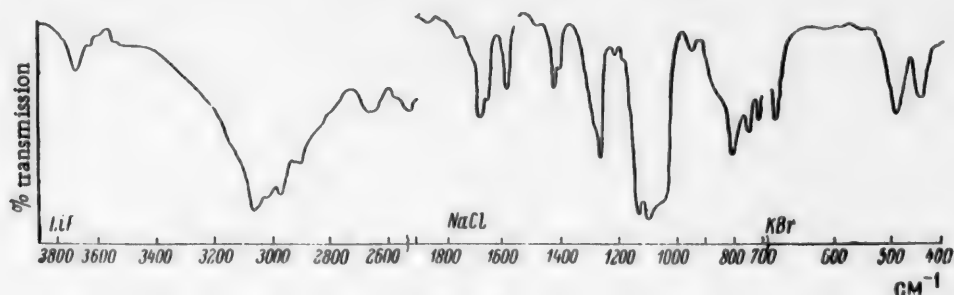


Fig. 1

In Fig. 2 is plotted the infrared absorption spectrum of the diketodicarboxylic acid (IV) in which the number (X) of methylphenylsiloxane groups is 3. The figure confirms the presence of the following groups in the compound:

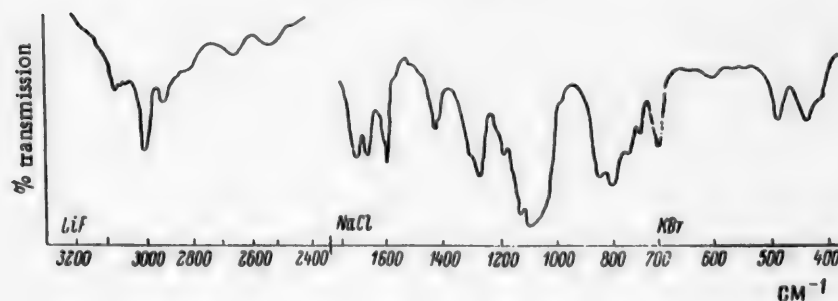
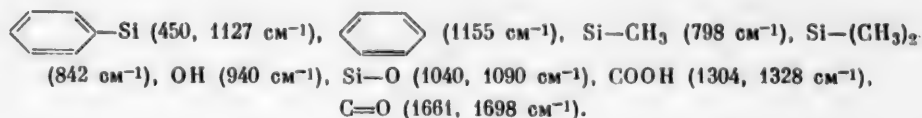


Fig. 2

EXPERIMENTAL

Synthesis of diketodicarboxylic silicoorganic acid (II) containing one methylphenylsiloxane group. 3-Phenyl-1,5-bis(o-carboxyphenylketobenzyl)pentamethyltrisiloxane. A mixture of 0.4 mole of anhydrous aluminum chloride, 0.2 mole of benzyldimethylchlorosilane, and 40 ml of chlorobenzene was put into a flask fitted with stirrer, thermometer, and reflux condenser. In the course of an hour 0.2 mole of phthalic anhydride was stirred intensively in small portions into the mixture. During this operation the temperature rose to 38-40° and hydrogen chloride was evolved. The mixture was then heated until hydrogen chloride ceased to come off. It was then cooled to 18-20°, 0.1 mole of methylphenyldichlorosilane was stirred in, and hydrolysis was effected with 20% hydrochloric acid at a temperature not exceeding 20°. The upper aqueous layer was separated and the lower layer evaporated in vacuo to constant weight at 120° (20 mm) and then treated with aqueous sodium carbonate solution. The resulting solution was filtered. After the filtrate had been acidified with hydrochloric acid, the product that separated was extracted with toluene. The extract was washed free of hydrochloric acid and analyzed after distillation of the solvent.

Found %: C 63.49; H 6.42; Si 11.29. M 811; acid number 130.8. $C_{41}H_{42}O_8Si_3$. Calculated %: C 65.90; H 5.67; Si 11.28. M 747; acid number 149.9.

The same procedure was applied to the preparation of the other diketodicarboxylic silicoorganic acids (II) except that the quantity of methylphenyldichlorosilane was varied during cohydrolysis. Acid (II) with X (number of methylphenylsiloxane groups) = 2 was obtained by carrying out the reaction with 0.2 mole of methylphenyldichlorosilane.

Found %: C 65.44; H 6.17; Si 12.24. M 982; acid number 108.3. $C_{48}H_{50}O_9Si_4$. Calculated %: C 65.30; H 5.71; Si 12.72. M 883; acid number 126.8.

With 0.3 mole of methylphenyldichlorosilane, acid (II) was obtained in which X = 3.

Found %: C 63.85; H 6.64; Si 13.82. M 1200; acid number 97.50. $C_{55}H_{58}O_{10}Si_5$. Calculated %: C 64.76; H 5.73; Si 13.77. M 1020; acid number 109.8.

Using 0.4 mole of methylphenyldichlorosilane, acid (II) was obtained with X = 4.

Found %: 63.55; H 6.20; Si 13.87. M 1220; acid number 92.03. $C_{62}H_{66}O_{11}Si_6$. Calculated %: C 64.42; H 5.75; Si 14.58. M 1156; acid number 96.8.

Reaction with 0.5 mole of methylphenyldichlorosilane gave acid (II) with X = 5.

Found %: C 64.00; H 6.00; Si 14.67. M 1280; acid number 79.60. $C_{69}H_{74}O_{12}Si_7$. Calculated %: C 64.14; H 5.77; Si 15.22. M 1292; acid number 86.7.

From 1.0 mole of methylphenyldichlorosilane we obtained acid (II) with X = 10.

Found %: C 63.10; H 6.10; Si 17.10. M 2000; acid number 46.52. $C_{104}H_{114}O_{17}Si_{12}$. Calculated %: C 63.31; H 5.82; Si 17.10. M 1973; acid number 56.7.

Synthesis of diketodicarboxylic silicoorganic acid (IV) containing one methylphenylsiloxane group (X = 1). 3-Phenyl-1,5-bis(carboxyvinylketobenzyl)-pentamethyltrisiloxane. Into a flask equipped with stirrer, thermometer, and reflux condenser were put 0.4 mole of anhydrous aluminum chloride, 0.2 mole of benzyldimethyldichlorosilane, and 50 ml of chlorobenzene. In the course of 35 min 0.2 mole of maleic anhydride was stirred into the mixture in small portions. During this operation the temperature was observed to rise to 40-45° and hydrogen chloride was released. After heating until hydrogen chloride was no longer evolved, the mixture was cooled; 0.1 mole of methylphenyldichlorosilane was added with stirring, and hydrolysis was effected with 20% hydrochloric acid at 4-10°. The product of cohydrolysis was extracted with toluene and washed free of hydrochloric acid. The solvent was driven off and the product analyzed.

Found %: C 59.30; H 6.06; Si 13.91. M 744; acid number 148.2. $C_{33}H_{38}O_8Si_3$. Calculated %: C 61.11; H 5.92; Si 13.03. M 647; acid number 173.1.

We used the same procedure when synthesizing other diketodicarboxylic silicoorganic acids (IV), only varying the quantity of methylphenyldichlorosilane during cohydrolysis. Operation with 0.2 mole of the latter gave acid (IV) containing two methylphenylsiloxane groups (i.e. X = 2).

Found %: C 58.97; H 6.89; Si 14.85. M 848; acid number 123.6. $C_{60}H_{46}O_9Si_4$. Calculated %: C 61.34; H 5.92; Si 14.35. M 783; acid number 143.0.

With 0.3 mole of methylphenyldichlorosilane, acid (IV) was obtained with $X = 3$.

Found %: C 60.16; H 6.89; Si 14.98. M 1219; acid number 113.6. $C_{47}H_{54}O_{16}Si_6$. Calculated %: C 61.4; H 5.92; Si 15.28. M 919; acid number 121.9.

With 0.4 mole of methylphenyldichlorosilane, acid (IV) was obtained with $X = 4$.

Found %: C 59.34; H 6.14; Si 16.85. M 1389; acid number 93.6. $C_{54}H_{62}O_{11}Si_6$. Calculated %: C 61.44; H 5.92; Si 15.96. M 1056; acid number 106.60.

With 0.5 mole of methylphenyldichlorosilane, acid (IV) was obtained with $X = 5$.

Found %: C 60.40; H 6.48; Si 16.69. M 1792; acid number 80.3. $C_{61}H_{70}O_{12}Si_7$. Calculated %: C 61.55; H 5.92; Si 16.48. M 1193; acid number 93.88.

With 1.0 mole of methylphenyldichlorosilane, acid (IV) was obtained with $X = 10$.

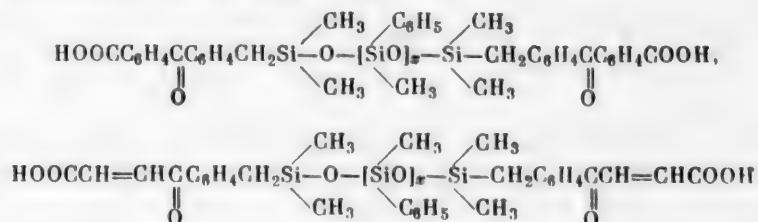
Found %: C 60.69; H 6.04; Si 17.91. M 1282; acid number 48.8. $C_{96}H_{110}O_{17}Si_{12}$. Calculated %: C 61.56; H 5.92; Si 18.00. M 1873; acid number 59.8.

SUMMARY

1. The aromatic ring of benzyldimethylchlorosilane can be acylated by maleic anhydride in presence of aluminum chloride.

2. It was shown that cohydrolysis of the products of acylation with various amounts of methylphenyldichlorosilane gives diketodicarboxylic silicoorganic acids containing various numbers of phenylsiloxane groups.

3. Silicoorganic diketodicarboxylic acids were synthesized



in which the numbers of methylphenylsiloxane groups (X) were 1,2,3,4,5,10. Their properties were determined.

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organic solvents. 2-Thienyl-(p-hydroxyphenyl)sulfone (VII) was prepared by oxidation of the benzoate (VIII) to sulfone (IX), which was then saponified.

Formylation of (III) gave 5-(p-methoxyphenylmercapto)-2-thiophenealdehyde (X) in 56% yield. Its structure was confirmed firstly by Kizhner reduction to sulfide (XI) and oxidation of the latter to sulfone (XII), and secondly by oxidation to the carboxylic acid (XIII). Sulfone (XII) and acid (XIII), obtained from 2-methylthiophene and from (X), do not differ in properties, and their mixed melting points are unchanged.

Consequently the sole product of formylation of (III) is the aldehyde (X). This result harmonizes with ideas about the Wilsmeier reaction as an electrophilic substitution reaction. Position 5 of the thiophene ring is actually the most reactive due to twofold activation: by the thiophenic sulfur and by the electron-donating p-methoxyphenylmercapto group in position 2. On the other hand the position ortho to the methoxy group in the benzene ring is insufficiently activated due to the uncoordinated orientation of the two first-order substituents: the methoxy group and the 2-thienylmercapto group [11].

The corresponding aldehyde could also be expected to be formed with facility on formylation of sulfide (V) since we know that treatment of resorcinol and its dimethyl ether with phosphorus oxychloride and dimethylformamide gave the aldehydes in approximately the same yields [12]. However, the aldehyde could not be isolated when (V) was formylated under the conditions employed for (III), the original sulfide being recovered to the extent of 55%.

5-(p-Hydroxyphenyl)-2-thiophenealdehyde (XIV) was obtained in small yield by formylation of the benzoyl derivative (VIII) and hydrolysis of the resulting aldehyde (XV). Wilsmeier formylation did not lead to entry of an aldehydic group into sulfones (VI) and (VII). Sulfone (VI), for example, was recovered unchanged to the extent of 97% after it had been treated with dimethylformamide and phosphorus oxychloride for 6 hr at 50° and 2 hr at 75°, and then held for two days at room temperature. Metalation of (VI) with n-butyllithium [13] and replacement of lithium by the formyl group by the action of dimethylformamide [14] led to two isomeric aldehydes, melting at 149° (XVI) and 91-92° (XVII) in the ratio of (XVI) : (XVII) \approx 1 : 1.2. The structure of the first aldehyde was established by oxidation to acid (XIII). Aldehyde (XVII) was also converted into an acid with m.p. 161-164° (XVIII), isomeric with acid (XIII). The position of the aldehyde group in (VII) and of the carboxyl group in (XVIII) has not yet been established. Constants, yields, and analyses of the compounds obtained in the present work are set forth in the table.

EXPERIMENTAL

2-Thienyl-(p-methoxyphenyl) sulfide (III). In the course of 30 min at 20° a solution of 72 g (1.127 moles) of n-butyllithium in 880 ml of ether was added to 94.7 g (1.127 moles) of thiophene in 120 ml of absolute ether. After it had stood for 30 min, the solution was cooled to -5°, and in the course of half an hour addition was made at this temperature of 36.06 g (1.127 g-atom) of dry sulfur powder (the sulfur was dried by distillation of the moisture with benzene). After the solution had been heated at the boil for an hour, it was cooled to 0°, and water (300 ml) was carefully stirred in. All operations were performed under argon. To the aqueous layer (separated from the ether layer at 30°), heated to 90°, was added the diazo solution with stirring. The latter was prepared from 147.6 g (1.2 moles) of p-anisidine, 300 ml of concentrated hydrochloric acid, 450 ml of water, and 82.8 g of sodium nitrite in 350 ml of water at 5-10° followed by neutralization with sodium acetate. After the diazo solution had been added, the mixture was heated on a water bath and allowed to stand overnight. It was then acidified with concentrated hydrochloric acid and 70 g of zinc dust was added. The mixture was then boiled for 2.5 hr. Reduction of the resulting dithienyl disulfide took place. The residue after steam distillation was extracted with ether. The ethereal extract was washed with 5% alkali solution, with hydrochloric acid, and finally with water, and then dried with magnesium sulfate. The solvent was distilled off and the residue distilled in vacuo. Yield of (III) 120.2 g (48.4%). B.p. 144-146° (1 mm), n_D^{20} 1.6362.

Compound (XI) was prepared by the same route from lithium 5-methyl-2-thienylmercaptide in 32% yield. B.p. 158-160° (0.5 mm), n_D^{20} 1.6248.

Dilution with methyl chloride of the residue after distillation of (III) led to deposition of 8.1 g of crystals (4% reckoned on p-anisidine). M.p. 120° (from methanol). According to the analytical data, the product is 2-(p-methoxyphenylmercapto)-5-(p'-methoxyphenyl)thiophene (IV).

2-Thienyl-(p-hydroxyphenyl) sulfide (V). An ethereal solution (461 ml) containing 46 g (0.72 mole) of n-butyllithium was stirred in the course of 30 min into 65 g (0.76 mole) of thiophene in 100 ml of absolute ether at a temperature not exceeding 20°. After stirring for 20 min, the mixture was cooled to 0° and a solution of 60.2 g (0.24 mole)

Compounds of the General Formula  X- Z

No.	X	Y	Z	Melting point	Boiling point (presure in mm)	Yield %	Empirical formula	Calculated (%)			Found (%)		
								C	H	S	C	H	S
III	H	S	OCH ₃	120°	144-146° (1)	48.4	C ₁₁ H ₁₀ OS ₂	59.42	4.54	28.85	59.43	4.78	29.02
IV	p-OCH ₃ C ₆ H ₄	S	OCH ₃	from alcohol	—	4	C ₁₈ H ₁₆ O ₃ S ₂ a	65.82	4.91	19.52	65.58	4.89	19.43
V	H	S	OH	53.5-54.5 from hexane	158-160 (1)	59	C ₁₀ H ₈ OS ₂	57.65	3.89	30.78	57.69	3.85	30.41
VI	H	SO ₂	OCH ₃	116-117 from aq. alcohol	—	85	C ₁₁ H ₁₀ O ₃ S ₂	51.98	3.96	25.21	52.28	4.26	25.11
VII	H	SO ₂	OH	181-182 from hexane	—	55	C ₁₀ H ₈ O ₃ S ₂	49.98	3.35	26.68	50.24	3.49	26.41
VIII	H	S	OCOC ₆ H ₅	75-76 from alcohol	—	90	C ₁₇ H ₁₂ O ₂ S ₂	65.35	3.87	20.53	65.55	3.87	20.01
IX	H	SO ₂	OCOC ₆ H ₅	162.5-163.5 from hexane	—	76	C ₁₇ H ₁₂ O ₄ S ₂	59.28	3.51	18.62	59.42	3.78	18.54
X	CHO	S	OCH ₃	64-65 from aq. alcohol	—	54	C ₁₂ H ₁₀ O ₃ S ₂ b	57.57	4.02	25.61	57.51	4.09	25.43
XI	CH ₃	S	OCH ₃	73.5-74.5	158-160 (0.5)	32	C ₁₂ H ₁₂ OS ₂ c	60.97	5.11	27.13	60.54	5.24	28.60
XII	CH ₃	SO ₂	OCH ₃	225-226 from aq. alcohol	—	66	C ₁₂ H ₁₂ O ₃ S ₂ c	53.71	4.51	23.89	53.83	4.59	23.58
XIII	COOH	SO ₂	OCH ₃	from aq. alcohol	—	100	C ₁₂ H ₁₀ O ₃ S ₂ d	48.31	3.38	21.49	48.52	3.48	21.29
XIV	CHO	S	OH	153-154 dichloromethane	—	56	C ₁₁ H ₈ O ₂ S ₂ e	55.91	3.41	27.14	55.83	3.67	27.06
XV	CHO	S	OCOC ₆ H ₅	84-85 from aq. alcohol	—	12.6	C ₁₈ H ₁₂ O ₃ S ₂ f	63.55	3.55	18.83	63.51	3.53	18.44
XVI	CHO	SO ₂	OCH ₃	148-149 from aq. alcohol	—	—	C ₁₂ H ₁₀ O ₄ S ₂	51.05	3.57	22.71	51.30	3.76	22.54
XVII	—	—	—	91-92 from hexane	—	—	C ₁₂ H ₁₀ O ₄ S ₂ g	51.05	3.57	22.71	51.28	3.57	22.30
XVIII	—	—	—	161-164 from aq. alcohol	—	—	C ₁₂ H ₁₀ O ₃ S ₂ h	48.31	3.38	21.49	48.09	3.32	21.22

Notes. a) Suggested structure; b) semicarbazone m.p. 198.5-199.5°, found %: N 13.59, 13.74, C₁₉H₁₅O₂N₃S. Calculated %: N 13.67; c) prepared from (XI); d) prepared from (X); e) semicarbazone m.p. 211-212°, found %: N 14.33, C₁₂H₁₁N₃O₃S₂. Calculated %: N 14.32; f) semicarbazone m.p. 208-209°; g) position of carbonyl group not established; h) position of carboxyl group not established.

of p,p'-dihydroxydiphenyl disulfide (m.p. 146-148°) [15] in 100 ml of absolute ether was added. After it had been stirred for an hour, the mixture was heated at the boil for 2 hr and then left overnight. The mass was poured into ice water and the ether layer collected and washed with 5% sodium hydroxide solution. An oil separated out on acidification of the alkaline layer and was extracted with ether. The ether extract was washed with water, with sodium bicarbonate solution and again with water, and dried with calcium chloride. The solvent was distilled off and the residue distilled in vacuo to give 14.34 g (47.4%) of thiohydroquinone with b.p. 102-106° (2 mm) and 29.45 g (59%) of (V) with b.p. 158-160° (1 mm). The product crystallized rapidly, and after three recrystallizations from hexane it was obtained in the form of slender needles with m.p. 53.5-54.5°.

2-Thienyl-(p-methoxyphenyl) sulfone (VI). Into a solution of 6.66 g (0.03 mole) of (III) in 50 ml of glacial acetic acid at 20° was stirred a solution of 10 g of potassium permanganate in 300 ml of acetone. The mixture was heated and stirred at 40° for 30 min, then treated with sodium bisulfite solution and diluted with water until precipitate ceased to come down. Yield of (VI) 6.47 g (85%). M.p. 116-117° (from dilute alcohol).

The same method was used for oxidation of (VIII) to (IX), of (XI) to (XII), and of (X) to (XIII).

2-Thienyl-(p-benzoyloxyphenyl) sulfide (VIII). Schotten-Baumann reaction of 8.56 g (0.0412 mole) of (V) with 5.5 ml of benzoyl chloride in 20 ml of 10% sodium hydroxide gave 11.45 g (90%) of (VIII) with m.p. 75-76° (from hexane).

2-Thienyl-(p-hydroxyphenyl) sulfone (VII). A mixture of 0.5 g of (IX), 5 g of sodium hydroxide and 50 ml of anhydrous methanol was boiled for 30 min. The cooled solution was acidified with 100 ml of phosphoric acid (d 1.04). After the benzoic acid had been distilled with steam, 0.2 g (55%) of (VII) came down; m.p. 181-182° (from aqueous alcohol).

5-(p-Methoxyphenylmercapto)-2-thiophenealdehyde (X). To a solution of 11.11 g (0.05 mole) of (III) in 20 ml of dimethylformamide was added 7.65 g (0.05 mole) of phosphorus oxychloride in 30 min at 0° with good stirring. The mass was then stirred at room temperature and allowed to stand overnight. The red solution was poured into 200 ml of saturated sodium acetate solution at 0°. The yellow precipitate was washed with water, 1 N HCl, bicarbonate solution, and again with water. Weight of dry product 6.76 g (54%); m.p. 64-65° (from hexane).

Semicarbazone; m.p. 198.5-199.5° (from aqueous alcohol).

5-Methyl-2-thienyl-(p-methoxyphenyl)sulfone (XII). A mixture of 2.5 g of (X), 8 ml of ethylene glycol, and 2 ml of hydrazine hydrate was shaken and heated until a yellow solution had formed. After addition of 2 g of potassium hydroxide, the mixture was heated at the boil for an hour. The oily layer was extracted with ether. The ether extract was washed with 10% hydrochloric acid, with sodium bicarbonate solution, and with water. Drying was then effected with magnesium sulfate and the solvent was removed. The resulting yellow oil, without distillation, was dissolved in acetone and oxidized with 10 g of potassium permanganate by the method described for (VI). There was obtained 1.22 g (45%) of (XII). M.p. 71-72°. A mixture with (XII) obtained from lithium 5-methyl-2-thienylmercaptide via (XI) did not exhibit a depression of melting point.

Found %: C 53.78, 53.51; H 4.54, 4.72; S 23.54, 23.28. $C_{12}H_{12}O_3S_2$. Calculated %: C 53.71; H 4.51; S 23.89.

5-(p-Methoxyphenylsulfonyl)-2-thiophenecarboxylic acid (XIII). a) Oxidation of 0.3 g of (XII) was effected with potassium permanganate (0.32 g of $KMnO_4$, 0.5 g of KOH, and 20 ml of water) at 95°. The filtrate was evaporated and acidified with 10% hydrochloric acid to give 0.02 g (6%) of (XIII) with m.p. 222-223° (from methanol).

Found %: C 48.44, 48.65; H 3.50, 3.32; S 21.31, 21.31. $C_{12}H_{10}O_6S_2$. Calculated %: C 48.31; H 3.38; S 21.49.

b) Oxidation of 0.5 g (0.0025 mole) of (X) was effected with 5 g of potassium permanganate by the method described for preparation of (VI). There was obtained 0.63 g of (XIII) (quantitative yield). M.p. 225-226° (from aqueous alcohol). No depression of melting point in a mixed melting test with (XIII) prepared from (XII).

c) To a solution of 0.09 g of (XVI) in 6 ml of glacial acetic acid was added 2 ml of 30% hydrogen peroxide. The mixture was heated on a boiling water bath for an hour and then left to stand overnight. The solution was filtered and the filtrate diluted with water to give 0.07 g (74%) of (XIII) with m.p. 223-224° (from dilute methanol). A mixture with (XIII) prepared from (XII) did not give a depression of melting point.

5-(p-Methoxyphenylsulfonyl)-2-thiophenealdehyde (XVI). An ethereal solution containing 0.96 g (0.015 mole) of n-butyllithium was added in the course of 15 min to 3.81 g (0.015 mole) of (VI) dissolved in a mixture of 110 ml

of absolute ether and 85 ml of anhydrous benzene at 5°. After stirring for 1.5 hr at 10-18° and for 10 min at the boil, addition was made at 5° of 2 g (0.03 mole) of dimethylformamide in 10 ml of absolute ether, and the mixture was left overnight under nitrogen. After boiling for an hour the mass was cooled and poured into ice water. The organic layer was separated and washed with dilute hydrochloric acid, sodium bicarbonate, and water. It was then dried over magnesium sulfate. The solid product (3.20 g) remaining after distillation of the ether was treated with concentrated sodium bisulfite solution. The solution was extracted with ether and benzene, and from the extracts we isolated 0.45 g (20%) of the original (VI). Addition of dilute hydrochloric acid to the bisulfite solution led to separation of a mixture of formyl derivatives (XVI and XVII) with m.p. 75-110°. The aldehyde (XVI) was isolated by fractional crystallization from alcohol. M.p. 148-149°.

A substance was isolated from the mother liquors after separation of (XVI). After several recrystallizations from alcohol, then from a mixture of hexane and benzene, and finally from benzene, the substance had m.p. 91-92° (XVII); it was isomeric with (XVI). The position of the formyl group was not established. The approximate ratio of (XVI) to (XVII) was 1:1.2.

Aldehyde (XVII) was oxidized to the carboxylic acid by the method used for preparation of (VI). M.p. of (XVIII) 161-164°.

5-(p-Benzoyloxyphenylmercapto)-2-thiophenealdehyde (XV). To a solution of 5.8 g (0.0186 mole) of (VIII) in 20 ml of dimethylformamide at 0° was added 1.83 ml (0.02 mole) of phosphorus oxychloride in the course of 15 min. The mass was stirred for an hour while the temperature rose to room temperature, and then for 3 hr at 70°. It was then left to stand for 60 hr at room temperature. The dark-red solution was poured into saturated sodium acetate solution. After the usual washings and drying, the precipitate weighed 5.69 g and had m.p. 48-78°. Its ethereal solution was shaken with concentrated sodium bisulfite solution for 20 hr. The precipitate was separated from the ethereal layer [from the latter was isolated 3.8 g (66%) of the original (VIII) with m.p. 63-67°] and washed with ether. The precipitate (insoluble in water) was heated for 15 min with dilute hydrochloric acid. An oil separated and crystallized after cooling. Yield 0.8 g (12.6%) of (XV) with m.p. 84-85° (from alcohol).

Semicarbazone: m.p. 208-209° (from aqueous alcohol).

5-(p-Hydroxyphenylmercapto)-2-thiophenealdehyde (XIV). A mixture of 0.44 g of (XV), 6 ml of concentrated hydrochloric acid, and 20 ml of glacial acetic acid was boiled for 3 hr. A green, crystalline product (0.28 g) came out after cooling and dilution with water; m.p. 102-130°. From this was recovered 0.09 g of (XV) with m.p. 74-80° after washing with cold 5% sodium hydroxide solution. Acidification of the alkaline filtrate with 5% hydrochloric acid gave 0.17 g (approximately 56%) of (XIV) with m.p. 153-154° (yellow crystals from CH₂Cl₂).

Semicarbazone: m.p. 211-212° (from aqueous alcohol).

SUMMARY

1. The following compounds, not previously described, were prepared: 2-thienyl-(p-methoxyphenyl) sulfide 5-methyl-2-thienyl-(p-methoxyphenyl) sulfide, their sulfones, and their formyl derivatives.

2. Wilsmeier formylation of 2-thienyl-(p-methoxyphenyl) sulfide gave 5-(p-methoxyphenylmercapto)-2-thiophenealdehyde.

3. Metalation of 2-thienyl-(p-methoxyphenyl) sulfone and replacement of the metal by the formyl group gave a mixture of two aldehydes, one of which was shown to have the structure of 5-(p-methoxyphenylsulfonyl)-2-thiophenealdehyde.

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THE INTERACTION OF NITRILES, TERTIARY ALCOHOLS, AND HYDROGEN CHLORIDE

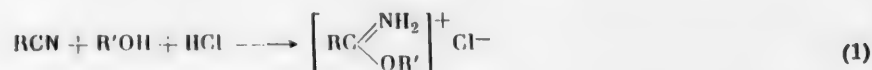
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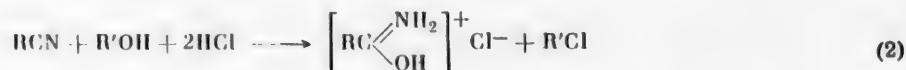
The well-known hydrohalides of imidoesters are formed by interaction of nitriles, hydrogen halides, and primary or secondary alcohols (reaction 1).



Nothing has been published about the reaction of nitriles, hydrogen halides, and tertiary alcohols. We know only that imidoesters are not formed in the reaction [1,2].

In the present work we studied the reaction in the cold between nitriles, tertiary alcohols, and hydrogen chloride.

It was found that the reaction very often gives tertiary alkyl chlorides and chlorides of iminohydrins (amide hydrochlorides) (reaction 2). These are also obtained by reaction of nitriles and hydrogen chloride with water [3,4] or with acids [5, 6].



Amide Hydrochlorides from Nitriles, Dimethylisobutylcarbinol, and Hydrogen Chloride

Expt. No.	Nitriles	Starting substances				Duration of experiment (in days)	Amide hydrochlorides			
		nitrile (in equiv.)	hydrogen chloride (in mole)	alcohol (in mole)	ether (in mole)		% Cl'	% N	yield (in %)	melting point (decomp.)
1	Acetonitrile	0.05	0.12	0.05	30	2			32	
2	" "	0.05	0.25	0.05	30	2			55	
3	" "	0.05	0.38	0.05	30	2			78	
4	" "	0.05	0.25	0.05	30	5			88	
5	" "	0.05	0.25	0.05	30	9	36.7	14.7	99	142 ¹
6	" "	0.15	Before saturation	0.15	—	1	36.5	14.7	92	142 ¹
7	" "	0.05	0.25	0.10	30	2			91	
8	" "	0.1	0.38	0.05	30	2			99	
9	Chloroacetonitrile	0.02	0.25	0.02	15	1	18.1	13.7	73 ²	
10	Adiponitrile	0.01	0.1	0.02	10	1	26.5	14.5	71 ³	
11	β-Chloropropionitrile	0.02	0.2	0.02	15	2	24.2	9.4	83	55—58 ⁴
12	Stearonitrile	0.01	0.1	0.01	20 ⁵	2			68	86 ⁶
13	Sebaconitrile	0.02	0.2	0.02	20	7	21.2	11.3	41 ³	
14	Benzonitrile	0.01	Before saturation	0.01	—	2	21.8	9.2	70	67 ⁷

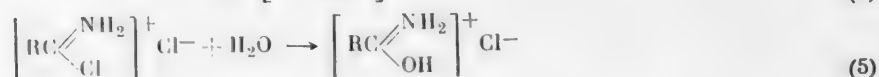
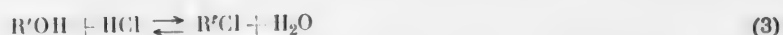
Notes. 1. Literature data [4]: 142°. 2. Mixture of chloroacetamide and its hydrochloride; yield calculated from nitrogen content of solid. 3. Mixture of hydrochlorides [5]; yield calculated from chlorine content of solid. 4. Literature data [4]: 50-60°. 5. Experiment carried out in toluene. 6. Literature data [4]: 85°. 7. Literature data [4]: 68°.

We see from the tabulated results that excess of any of the starting components accelerates reaction (2). The rate of formation of amide hydrochlorides decreases with changing character of radical R in approximately the same sequence as was observed for hydration of nitriles with water in presence of hydrogen chloride [4].

Some nitriles (ethoxypropionitrile, capronitrile) did not give iminohydrin chlorides after prolonged standing with hydrogen chloride and a tertiary alcohol. Results similar to those obtained with dimethylisobutylcarbinol (set forth in the table) were obtained in reactions with nitriles of trimethylcarbinol, dimethylethylcarbinol, dimethylpropylcarbinol, and other tertiary alcohols.

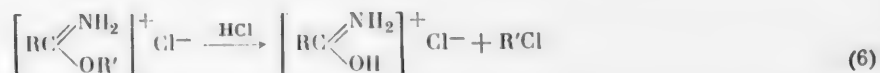
It was found that different reactions can predominate during preparation of the chlorides, depending on the nature of the starting nitrile and the experimental conditions.

It is widely assumed [7] that reaction of alcohols with hydrogen chloride according to equation (3) initially gives an oxonium ion which subsequently undergoes scission at the carbon-oxygen bond into water and carbonium ion; the latter is stabilized by reaction with chloride ion. In the case of tertiary alcohols, reaction (3) goes with relative facility. It is logical to assume that the liberated water can react with the products of reaction of nitriles with hydrogen chloride, for example with immonium chloride chlorides (equation 4) with formation of amide hydrochlorides [3] (equation 5).



However, since tertiary alcohols do not react in the cold to any substantial extent with hydrogen chloride (equation 3) when heavily diluted with inert solvent, while amide hydrochlorides and alkyl halides are nevertheless formed in presence of nitriles, it becomes necessary to seek for another mechanism to explain reaction (2).

A second possible mechanism for reaction (2) involves initial reaction of nitriles and hydrogen chloride with tertiary alcohols in the same way as with primary and secondary alcohols, i.e. with formation of imidoester hydrochlorides (reaction 1). Due to the presence of hydrogen chloride, however, the Pinner rearrangement [8, 9] subsequently takes place



The latter reaction is usually effected by heating of the imidoester salts in the absence of free hydrogen chloride, and therefore the products are not the amide hydrochlorides but the free amides. Reaction (6) also accounts for the formation of amides instead of imidoester salts on reaction of trichloroacetonitrile with alcohols and hydrogen chloride [9]. The formation in the present reaction and in other reactions [4] with trichloroacetonitrile not of the hydrochloride but of the free amide is evidently due to the considerable negative inductive effect brought about by the three chlorine atoms, which cause the nucleophilic properties of the amide oxygen to be so weakened that it becomes incapable of attracting a proton.

According to a third possible mechanism of reaction (2), the direct products of interaction of nitriles and hydrogen chloride and, in particular, immonium chloride chlorides (reaction 4) lead to replacement of the hydroxyl group of the tertiary alcohol by a chlorine atom. This postulate is based on the work of Seikina [10] who showed that quaternary ammonium salts in reactions with alcohols exhibit dehydrating properties through intermediate formation of oxonium complexes. Heating of alcohols with pyridine hydrochloride, for example, converts them into mixtures of olefins, alkyl halides and ethers. We may therefore suggest that immonium chloride chlorides (or other products of interaction of nitriles and hydrogen chloride with enhanced electrophilic reactivity) can also bring about dehydration of alcohols and that the process will proceed with particular facility in the case of tertiary alcohols. The initial step in reaction of immonium chloride with an alcohol may be schematically represented [10] by equation (7), according to which the deprotonized immonium chloride is split into the starting components.



The resulting oxonium ion is further cleaved to give a carbonium ion and a molecule of water. The latter then reacts with the nitrile and hydrogen chloride as in reactions (4) and (5).

Finally, we may attribute the stability of tertiary alcohols in presence of hydrogen chloride and certain nitriles with a high measure of probability to weak interaction of these nitriles with hydrogen chloride under the experimental conditions, i.e. they do not give electrophilic compounds capable of removing water from alcohols.

A study was also made of the interaction of acetonitrile, adiponitrile, and chloroacetonitrile (which differ in reactivity) with hydrogen chloride and a secondary alcohol (cyclohexanol). Experiments were run under the conditions of formation of immoniumhydrin chlorides from nitriles, tertiary alcohols, and hydrogen chloride. Each of the three nitriles behaved differently. Acetonitrile did not react in excess of solvent with secondary alcohols (although in the absence of solvent the reaction goes with formation of iminoether salts [11]). Adiponitrile gave a nearly quantitative yield of the dicyclohexyl imido adipate hydrochloride. The precipitate from a solution of chloroacetonitrile, cyclohexanol, and hydrogen chloride in ether consisted (as in the case of tertiary alcohols) of a mixture of chloroacetamide and its hydrochloride. On the other hand, if hydrogen chloride was passed into cyclohexanol and chloroacetonitrile in the absence of solvent, the reaction mixture very quickly solidified completely with formation of the cyclohexyl imido chloroacetate hydrochloride (reaction 1). This salt could be kept substantially unchanged under ether saturated with hydrogen chloride for a week at 0° under normal conditions. In our experiments, therefore, chloroacetamide hydrochloride is not a product of cleavage of the corresponding iminoester hydrochloride according to reaction (6) but was probably formed by the third mechanism.

In conclusion, the authors thank M. M. Bershtein for assistance during the work.

EXPERIMENTAL

The starting substances were the nitriles prepared earlier [4]. Tertiary alcohols were synthesized from the corresponding ketones and organomagnesium compounds. Dimethylisobutylcarbinol had d_4^{20} 0.8120, n_D^{20} 1.4173; dimethylpropyl carbinol had d_4^{20} 0.8313, n_D^{20} 1.4119 in agreement with the literature [12].

Acetimmoniumhydrin chloride and 2-chloro-2,4-dimethylpentane. a) Experiment 6. A mixture of 6.15 g of acetonitrile and 17.4 g of dimethylisobutylcarbinol at 0° was saturated with hydrogen chloride. The following day 13.2 g of acetimmoniumhydrin chloride was filtered from the reaction mixture; m.p. 142° (decomp.); hydrolysis gave acetamide [4]. The filtrate (17.5 g) was washed with water, with weak bicarbonate solution, and again with water, dried over calcium chloride, and fractionally distilled. There was obtained 13.0 g (60%) of 2-chloro-2,4-dimethylpentane.

B.p. 128° (750 mm), n_D^{20} 1.4190, d_4^{20} 0.8600. Literature [13]: b.p. 52° (46 mm), n_D^{20} 1.4180, d_4^{20} 0.8601.

Found %: Cl 25.8. $C_7H_{15}Cl$. Calculated %: Cl 26.2.

b) Experiment 5. Hydrogen chloride (9 g) was passed into a solution of 2.15 g of acetonitrile and 5.8 g of dimethylisobutylcarbinol in 30 ml of absolute ether. After the lapse of 9 days, acetimmoniumhydrin chloride (4.7 g) was filtered off; fractional distillation of the mother liquor gave 2.7 g of 2-chloro-2,4-dimethylpentane identical with the product of experiment 6.

c) The same alkyl chloride was also obtained when hydrogen chloride was passed into the carbinol at 0°. The alkyl chloride was not formed when hydrogen chloride was passed into a 10% solution of dimethylisobutylcarbinol in ether.

Acetimmoniumhydrin chloride and 2-chloro-2-methylpentane. From a mixture of 2.15 g of acetonitrile and 5.1 g of dimethylpropylcarbinol in 15 ml of ether saturated with hydrogen chloride in the course of 24 hr at 5° was obtained 4.4 g of acetimmoniumhydrin chloride. From the filtrate was isolated 2.5 g of 2-chloro-2-methylpentane.

B.p. 62° (150 mm), n_D^{20} 1.4132, d_4^{20} 0.8621. Literature [14]: b.p. 105-107° (746 mm), n_D^{20} 1.4128, d_4^{20} 0.8610.

Dicyclohexyl imido adipate hydrochloride. Hydrogen chloride (27 g) was passed into a solution of 5.4 of adiponitrile and 10.0 g of cyclohexanol in 30 ml of ether at 0°. Dicyclohexyl imido adipate hydrochloride (19 g) was filtered after three days; m.p. 138-140° (decomp.) (from acetic acid and ether).

Found %: Cl 18.7; N 7.4. $C_{18}H_{34}O_2N_2Cl_2$. Calculated %: Cl 18.6; N 7.35.

The salt (10 g) was dissolved in the cold in water and neutralized with weak potassium carbonate solution. After an hour, 7.4 g (91%) of dicyclohexyl imidoadipate was filtered off m.p. 37°; literature [15]: 36°.

Interaction of chloroacetonitrile, hydrogen chloride, and cyclohexanol. a) From 11.4 g of chloroacetonitrile, 15.1 g of cyclohexanol, and 14 g of hydrogen chloride in 40 ml of ether in the course of 6 days at 12° was obtained 3.0 g of a mixture of chloroacetimmoniumhydrin chloride and chloroacetamide. The product (2.0 g) was dissolved in water and neutralized with potassium carbonate solution. The resulting precipitate (1.35 g) had m.p. 120° and did not give a depression with authentic chloroacetamide.

Hydrogen chloride and ether were distilled from the mother liquor after separation of the chloroacetimmoniumhydrin. An oily product came down (4.8 g) which after recrystallization from water melted at 119° and was identical with the chloroacetamide described above. Continuation of the fractional distillation yielded two fractions: 70-130° (2.6 g) and 130-144° (2.9 g). The residue weighed 2.3 g. Redistillation of the 2nd fraction gave 1.6 of cyclohexyl chloride.

B. p. 142°, n_D^{20} 1.4611; literature [12]: b.p. 142°, n_D^{20} 1.4626.

b) The product formed by saturation with hydrogen chloride of equimolar quantities of chloroacetonitrile and cyclohexanol solidified completely within an hour. The resulting hydrochloride of the cyclohexyl iminoester of chloroacetic acid was dissolved in acetic acid and precipitated by ether.

Found %: Cl⁻ 16.5; N 6.3. $C_{18}H_{35}ONCl_2$. Calculated %: Cl⁻ 16.8; N 6.6.

Hydrolysis of 7 g of salt gave 5.2 g of cyclohexyl chloroacetate.

B.p. 119° (20 mm), n_D^{20} 1.4680, d_4^{20} 1.1379, MR_D 43.14; calc. 43.46.

Literature [16]: b.p. 101-102° (11 mm).

SUMMARY

1. It was shown that chlorides of immoniumhydrins (amide hydrochlorides) and tertiary alkyl chlorides are formed on interaction of nitriles, hydrogen chloride, and tertiary alcohols.

2. Possible reaction mechanisms are considered. It is suggested that chlorides of immoniumhydrins are formed by addition of water to products of interaction of nitriles with hydrogen chloride. The water can be derived from reaction of tertiary alcohols with hydrogen chloride or with electrophilic products of interaction of the latter with nitriles. Chlorides of immoniumhydrins are probably also products of cleavage of the initially formed hydrochlorides of imidoesters. One mechanism or the other may predominate, depending on the character of the starting components and on the reaction conditions.

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COMPARISON OF BROMIDES AS CATALYSTS OF DEUTEROEXCHANGE OF AROMATIC COMPOUNDS WITH LIQUID DEUTERIUM BROMIDE

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Very little information has been published about the acidic catalysis of isotopic hydrogen exchange in CH bonds of organic compounds. This paper is the follow-up to a short note on this subject [1].

Polanyi et al. [2] and Klit and Langseth [3] established that deuterioexchange between HCl and benzene is catalyzed by $AlCl_3$. The analogous reaction in liquid DBr is catalyzed by $AlBr_3$ [4]. We have now compared the catalytic activity of a series of bromides and have found that the activity declines in the sequence: $AlBr_3 \geq GaBr_3 > FeBr_3 \gg BBr_3 > SbBr_3 > TiBr_4 \gg SnBr_4$. $InBr_3$ is an active catalyst. Formation of a stable complex between catalyst and substrate (nitrobenzene, benzoic acid) suppresses deuterioexchange, just as other electrophilic hydrogen substitution reactions in aromatic compounds are suppressed.

The results are of interest for characterization of the relative activity of Friedel-Crafts catalysts and for interpretation of the mechanism of acidic hydrogen exchange in aromatic compounds.

EXPERIMENTAL

Preparations. The following bromides were synthesized from the elements*: BBr_3 [5] (-46.9°), $AlBr_3$ [6,7] (97.5°), $GaBr_3$ [8] (120.3°), $InBr_3$ [7,9], $SnBr_4$ [7] (30.5°), $SbBr_3$ [2] (96.6°), $FeBr_3$ [10]. $TiBr_4$ (39.5°) was prepared by reaction of bromine with a mixture of TiO_2 and carbon [7,11]. Excess of bromine was removed from the bromides by blowing with dry nitrogen or carbon dioxide. In the case of BBr_3 bromine was removed by vigorous shaking with mercury. All of the substances (except $FeBr_3$) were distilled several times in vacuo ($AlBr_3$ over Al, $SbBr_3$ over Sb). The bromides were sealed in vacuo into ampoules with a thin-walled concave base. All of the substances except $TiBr_4$ and $FeBr_3$ were perfectly colorless. Direct comparison of the catalysts, which differed considerably in activity, was made possible by the selected method of charging accurately weighed samples of bromide into thin-walled glass bulbs and by the procedure for sealing them in the containers without contact with atmospheric moisture [12].

Benzene (cryoscopic grade) was distilled over metallic sodium. Samples of benzene were weighed in the dry compartment into thin-walled, small ampoules illustrated in Fig. 3 of paper [13]. Benzoic acid (Kahlbaum) was sublimed several times in vacuo (m.p. 123°). Nitrobenzene (Kahlbaum) was dried over $CaCl_2$ and distilled several times in vacuo (b.p. 210° , n_D^{20} 1.5515).

Experimental procedure. Deuterium-containing liquid hydrogen bromide** was prepared in the apparatus described earlier [13]. The test tubes for the catalytic experiments had the altered shape and dimensions shown in the figure. On the rim of the test tube was placed a spiral glass mallet onto which was carefully lowered the concave-bottomed ampoule containing the weighed sample of catalyst. The small ampoule containing the weighed sample of benzene or other substance was then introduced. After the test-tubes had been filled with liquid DBr, they were sealed off from the apparatus and placed in a thermostat ($25 \pm 0.1^\circ$) or cryostat [14] ($-21 \pm 1^\circ$). The ampoules containing the substance were crushed by raising the vapor pressure of the solvent, and the catalyst ampoules were broken with the help of the mallet (shaking of the test-tube).

*The formulas of the bromides are given in their simplest forms, e.g. $AlBr_3$ instead of Al_2Br_6 . Melting points are given in parentheses (mean of 3-7 measurements) and were determined in absence of atmospheric moisture.

**We designate this arbitrarily as DBr.

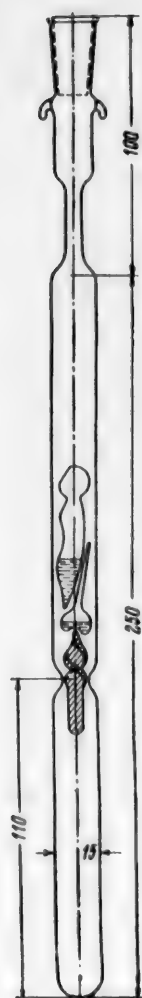


TABLE 1. Experiments with Benzene

$C \cdot 10^4$	τ (min)	n	$h \cdot 10^4$	$\frac{h \cdot 10^4}{C \cdot 10^4}$
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Catalyst $AlBr_3$

2	60	0.2	8	4
3	60	0.1	5	2
3	30	0.1	10	3
4	30	0.1	10	2
5	10	0.2	56	12
7	10	0.2	46	7
8	30	0.2	22	3
11	10	0.4	127	12
12	30	0.4	36	3
14	10	0.6	169	12
16	10	0.2	69	4
17	10	0.5	138	8
20	30	1.5	155	8
22	30	3.4	468	21
78	30	5.4	2530	33
97	30	5.5	1400	14
13*	60	2.6	160	12
24*	60	2.0	110	5
36*	30	3.1	400	11
80*	30	2.0	850	11

Catalyst $GaBr_3$

14*	60	2.3	140	10
18*	60	4.0	300	4
51*	60	3.9	300	6
102*	30	4.1	640	6

TABLE 2. Experiments with Benzene

$C \cdot 10^4$	τ (min)	n	$h \cdot 10^4$	$\frac{h \cdot 10^4}{C \cdot 10^4}$
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Catalyst $FeBr_3$

0.9*	30	0.3	27	30
2.0*	60	0.8	40	19
3.0*	30	0.4	35	11
9.5*	60	3.4	235	25
14.0*	30	1.8	200	15

TABLE 3. Experiments with Benzene

$C \cdot 10^3$	τ (hr)	n	$h \cdot 10^4$	$\frac{h \cdot 10^4}{C \cdot 10^3}$
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Catalyst BBr_3

0.6	5	0.6	6	10
0.8	3	0.6	9	12
0.8	1	0.3	12	14
0.8	3	0.7	10	12
0.8	1	0.3	12	14
0.8	3	0.7	10	12
0.9	3	0.9	15	16
0.9	3	0.6	10	11
1.0	3	0.7	11	11
1.0	5	0.9	9	9
1.0	6	1.8	7	17
1.1	5	1.0	10	9
1.1	3	0.8	13	11
1.3	3	0.8	14	11
1.3	6	2.4	23	18
1.3	3	0.8	14	11
1.6	3	1.1	18	11
2.3	3	1.3	23	10
2.3	3	1.4	25	11

TABLE 4. Experiments with Benzene

$C \cdot 10^4$	τ (hr)	n	$h \cdot 10^4$	$\frac{h \cdot 10^4}{C \cdot 10^4}$	$C \cdot 10^3$	τ (hr)	n	$h \cdot 10^4$	$\frac{h \cdot 10^4}{C \cdot 10^3}$
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Catalyst $SbBr_3$

1.4	24	0.8	2	1
1.7	24	1.1	2	1
1.8	48	3.9	6	3
1.8	24	1.3	3	2
1.9	24	1.4	3	2
2.0	24	2.9	8	4
2.1	24	2.4	6	3
2.5	48	4.3	7	3
2.8	66	4.3	5	2
2.9	160	5.7	5	2

Catalyst $TiBr_4$

0.2	72	0.3	0.2	0.8
0.4	72	0.3	0.2	0.5
0.4	160	0.5	0.1	0.4
0.5	72	0.3	0.2	0.5
0.6	15	0.1	0.2	0.3
0.6	160	1.3	0.4	0.8
0.7	160	0.6	0.2	0.3
0.8	72	0.4	0.3	0.4
0.8	72	0.4	0.3	0.4
0.8	160	0.8	0.3	0.3
1.0	72	0.5	0.3	0.3
1.1	72	0.6	0.4	0.4
1.3	160	1.1	0.3	0.3
1.3	160	1.0	0.4	0.3
1.5	72	0.7	0.5	0.3
1.6	72	0.9	0.6	0.4

TABLE 5. Experiments with Benzene

$C \cdot 10^3$	τ days	n	$k \cdot 10^3$
Catalyst SnBr_4			
0.1	7	0.2	4.4
0.5	7	0.2	4.2
0.7	25	0.5	4.3
1.1	25	0.6	4.7
2.0	7	0.2	4.4
Without catalyst			
	7	0.2	4.6
	25	0.6	4.6
	25	0.6	4.7

TABLE 6. Mean Values of $k \cdot 10^3/C \cdot 10^3$ in Experiments with Benzene

Catalyst	$k \cdot 10^3/C \cdot 10^3$
AlBr_3	100000*
GaBr_3	70000*
FeBr_3	2000*
BBr_3	12
SbBr_3	2
TiBr_4	0.4

TABLE 7. Experiments with Nitrobenzene (Catalyst AlBr_3)

$C \cdot 10^3$	$C_1 \cdot 10^3$	$C' \cdot 10^3$	τ (hr)	n	$k \cdot 10^3$	$k \cdot 10^3/C' \cdot 10^3$
0.1	2.8	—	49	0	—	—
0.6	3.3	—	49	0	—	—
1.0	3.2	—	49	0	—	—
1.4	2.1	—	474	0	—	—
2.0	3.1	—	474	0	—	—
2.3	1.8	0.5	165	0.1	9	18
2.1	1.1	1.0	165	0.2	16	16
2.3	1.0	1.3	165	0.2	17	13
2.3	0.9	1.4	330	0.3	6	4
2.4	0.9	1.5	330	0.3	5	3

TABLE 8. Experiments with Benzoic Acid (Catalyst AlBr_3)

$C \cdot 10^3$	$C_1 \cdot 10^3$	$C' \cdot 10^3$	τ (hr)	n	$k \cdot 10^3$	$k \cdot 10^3/C' \cdot 10^3$
1.7	2.1	—	24	0.1	—	—
1.7	2.0	—	20	0.1	—	—
1.9	1.9	—	24	0.1	—	—
1.9	1.9	—	24	0.1	—	—
2.2	2.2	—	24	0.1	—	—
1.4	1.2	0.2	52	1.8	2	10
1.8	1.2	0.6	24	1.9	6	10
2.9	2.0	0.9	49	3.8	8	9
2.3	1.1	1.2	24	2.8	10	8
2.1	0.9	1.2	24	2.7	9	8

At the conclusion of an experiment, the test tube containing the solution was immersed in a Dewar flask (liquid air-cooled) and opened. The solvent was sucked out by a water jet pump. Aqueous alkali (6 N) was then added, and the supernatant benzene was withdrawn with a pipet and distilled in vacuo over sodium powder. Benzoic acid was isolated by addition of water and extraction with ether. After the ether had been driven off, the acid was sublimed several times in vacuo. The ethereal solution of nitrobenzene was dried over CaCl_2 . After the ether had been removed, the nitrobenzene was distilled several times in vacuo. The constants of the substances were found to remain unchanged during an experiment.

The substances were burned, and the deuterium concentration in the purified water of combustion was determined by the drop method [15]. The number of hydrogen atoms exchanging with deuterium was calculated by the method of [16]. The rate constant of the exchange reaction was calculated by means of a first order equation.

Experimental results for hydrogen exchange are set forth in Tables 1-8 in which the following symbols are used:

C —catalyst concentration in moles per mole HBr ; C' —catalyst concentration in excess of the stoichiometric requirement for the substrate; C_1 —concentration of aromatic compound in moles per mole HBr ; n —number of hydrogen atoms in molecules of substance exchanging with deuterium; k —rate constant of deuterioexchange of the monomolecular reaction (sec^{-1}); k/C —rate constant referred to catalyst concentration.

In the different experiments the weight of solvent varied between 12 and 24 g; the weight of the benzene sample was between 0.5 and 0.8 g; that of the benzoic acid sample was between 0.2 and 0.6 g; that of the nitrobenzene sample was between 0.2 and 0.8 g. Weights of catalyst varied between 0.0001 and 2 g, depending on the activity of

the bromide.* In the tables in order to save space, only the concentration of catalyst in solution is given. The concentration of benzene, benzoic acid, and nitrobenzene in solution varied respectively in the ranges $(2.4-4.4) \cdot 10^{-2}$, $(0.6-2.6) \cdot 10^{-2}$, and $(0.6-3.3) \cdot 10^{-2}$ moles/mole HBr. Experiments at -21° are marked with an asterisk. Experiments extending over more than 72 hr were carried out at room temperature.

The solubility of InBr_3 in liquid HBr at 25° is less than 0.3 g/100 g HBr. It is such a strong catalyst, however, that even this concentration is accompanied by rapid exchange of the hydrogen in benzene. SnBr_4 has substantially no catalytic influence on the isotopic exchange of hydrogen between benzene and DBr. This was demonstrated in comparative experiments without a catalyst and with addition of from 0.001 to 0.02 mole of SnBr_4 per mole of HBr. These experiments were run in parallel and the rate constants were identical within the limits of experimental error: $4.4 \cdot 10^{-8}$ and $4.6 \cdot 10^{-8} \text{ sec}^{-1}$.**

Table 6 shows mean values of relative rate constants of exchange of hydrogen in benzene in presence of different catalysts ($k \cdot 10^6 / C \cdot 10^2$). The scale of catalytic activity of bromides obtained on this basis is very wide: The relative rate constants at the two extremes differ by more than five orders of magnitude. This is consistent with the strongly differentiating properties of liquid HBr, which is characterized by a low dielectric constant ($\text{DC} = 4$ at 25°) [19].

DISCUSSION OF RESULTS

Formation of ternary complexes of the type of $\text{ArH} \cdot \text{DBr} \cdot \text{MBr}_n$ is possible when bromides dissolve in liquid DBr in presence of aromatic hydrocarbons (ArH). In these complexes the D-Br bond is polarized due both to the coordinative unsaturation of the central atom of the bromide and to the proton and deuteron affinity (P) of the hydrocarbon molecule. With a sufficiently high energy of the coordinative bond between metal and bromine ion, especially when P increases, polarization of the bond may be effected by ionization: A deuteron may add on to the aromatic hydrocarbon molecule to form a carbonium ion (ArHD^+), while the addition of a bromine ion to the bromide leads to a complex anion (MBr^-_{n+1}). Subsequent detachment of a proton from the carbonium ion leads to rapid hydrogen exchange [20-23].

Ternary complexes of aluminum bromide and gallium bromide are strongly polar [24]. Judging by measurements by P. P. Alikhanov in our laboratory, the addition of AlBr_3 to a solution of an aromatic hydrocarbon in liquid HBr considerably increases the specific electrical conductivity of the solution. In the case of mesitylene, for example, it increases by four orders of magnitude to $10^{-4} \text{ ohm}^{-1} \text{ cm}^{-1}$. In the absence of a hydrocarbon a 0.1 molar solution of AlBr_3 in liquid HBr is a very poor conductor of electricity ($\kappa = 2 \cdot 10^{-7} \text{ ohm}^{-1} \text{ cm}^{-1}$). The exceptionally rapid exchange of hydrogen in presence of AlBr_3 and GaBr_3 is determined by the high degree of polarization of the D-Br bond. An approximately ionic mechanism of exchange is then involved.

Decreasing electrophilic character of the halide is accompanied by a fall in concentration and polarity of the molecular compound [25]. The number of ions and ionic associates in solution steadily decreases, and un-ionized complexes predominantly participate in the reaction [22]. The exchange reaction proceeds mainly by an associative, molecular mechanism.

Change of mechanism of a given heterolytic reaction from ionic to associative and the overlapping of these two mechanisms in dependence on the activity of the catalyst are reflected in a subsequent change in the rate constant of the reaction by more than five orders of magnitude. This provides further support for the view that intermediate mechanisms are possible in addition to the S-1 and S-2 mechanisms of hydrogen exchange [23, 26]. Similar views are now becoming more and more popular [27-29] in connection with chemical reactions of electrophilic replacement of hydrogen in aromatic compounds (e.g. alkylation) as well as of nucleophilic substitution [30, 31].

The catalytic activity of a halide depends on the magnitude of the bonding energy between the central halide atom and the halide ion [32]. We do not possess corresponding data for the compounds considered in the present paper. An indication of the relative strength of donor-acceptor interaction between halide and electron donor is given, however, by the following bond energies (given in kcal/mole) resulting from reaction between benzaldehyde and chloride in the gas phase (calculated on the basis of some simplifying assumptions [33]).



* The experimental accuracy is reduced at the lowest catalyst concentrations.

** We may mention that SnCl_4 catalyzes the exchange of tritium between TCl and toluene, and the rate of exchange is proportional to the SnCl_4 concentration [17]. This difference in our experiments may be due to toluene possessing a very much higher reactivity than benzene [18].

This sequence of chlorides resembles that established in the present work for the bromide series (an exception is the position of the antimony compound).

The theory of participation of ternary complexes in the exchange reaction is also made plausible by the fact that the reaction practically does not take place if one of the components of the complex is omitted. This point is illustrated by isotopic hydrogen exchange experiments involving nitrobenzene and benzoic acid (Tables 3 and 4). Menshutkin [34] had established the formation of a molecular compound of nitrobenzene with AlBr_3 by physicochemical analysis [34]. Other methods confirmed his observation (for literature see [35]). Other halides form similar compounds with nitrobenzene [36]. Nitro compounds are very weak bases in which a proton is attached to the nitro group. According to Hammett [37] the dissociation constant of nitrobenzene in water is of the order of 10^{-24} – 10^{-25} . In solution in anhydrous sulfuric acid, on the other hand, nitrobenzene is 41% ionized [38]. When nitrobenzene and aluminum bromide are jointly dissolved in liquid hydrogen bromide, there is a possibility of formation of a compound of the type of $\text{C}_6\text{H}_5\text{NO}_2 \cdot \text{HBr} \cdot \text{AlBr}_3$, which differs from the above type of ternary complex by having a proton attached to the nitro group and not to the aromatic ring.

We see from Table 3 that not only does hydrogen exchange not take place in nitrobenzene when the quantity of AlBr_3 is nearly in stoichiometric ratio to the nitrobenzene in solution, but the rate of exchange is very small when AlBr_3 is in excess. This is probably due not only to the passivating influence of the nitro group on deuteroexchange in the ring, but also to the presence of a positive charge on the substance [21b, 23]. The structure of the positively charged ion might be represented as follows [38]:



Acidic exchange of hydrogen in aromatic compounds is subject to the laws of electrophilic substitution [20, 23]. It is well known that formation of molecular compounds between nitrobenzene and AlBr_3 (and other acidic halides) markedly lowers the rate of electrophilic substitution of hydrogen, for example in bromination [39]. Nitrobenzene also inhibits the isotopic exchange of radiobromine between AlBr_3 and $\text{C}_2\text{H}_5\text{Br}$ [35, 40].

Benzoic acid, like nitrobenzene, is capable of manifesting the properties of a weak base [37, 41]. If the quantity of AlBr_3 exceeds the stoichiometric requirement for benzoic acid, then the hydrogen in the aromatic ring of the latter exchanges with DBr to an extent approximately proportional to the AlBr_3 concentration. The rate constant k/C' is two orders of magnitude larger than in hydrogen exchange in nitrobenzene, and four orders smaller than in exchange experiments with benzene. Exchange inhibition may here be explained in terms of the same causes that were mentioned in the discussion of results with nitrobenzene.

What has been said above is also consistent with the nearly complete absence of exchange of hydrogen in nitrobenzene and in the ring of benzoic acid with liquid deuterium fluoride [42]. Solutions of both substances in this solvent are known to be good conductors of an electric current due to formation of organic cations [43]. Isotopic exchange of hydrogen between nitrobenzene and sulfuric acid is also greatly retarded [44].

It is interesting to compare the sequence of catalytic activity of bromides in deuteroexchange with liquid DBr with the literature data for the relative strength of bromides and chlorides of the same elements as generalized acids (acidlike substances [45]). In this connection we must bear in mind the specificity of reactions between generalized acids and bases emphasized by Lewis [46], which usually makes it difficult to arrange the generalized acids in a unitary series in order of their strengths.

It must also be taken into consideration that the data presented below are not strictly comparable because some authors evaluate the relative activity of catalysts from the yield of reaction product while others measure the reaction rate. Different kinetic orders are sometimes observed in presence of different catalysts, and there are also appreciable individual differences in the relative strength of bromides and chlorides in a given reaction.

- I. Friedel – Crafts reactions [47]
 $\text{AlCl}_3 > \text{FeCl}_3 > \text{SnCl}_4 > \text{TiCl}_4$
- II. Bromination of toluene [48]
 $\text{AlBr}_3 > \text{FeBr}_3 > \text{SnBr}_4$
- III. Alkylation of aromatic hydrocarbons [49]
 $\text{AlBr}_3 > \text{GaBr}_3$

- IV. Friedel - Crafts acylation of toluene [50-52]
 $\text{AlCl}_3 > \text{FeCl}_3 > \text{TiCl}_4 > \text{SnCl}_4$
 $\text{AlBr}_3 (83) > \text{FeBr}_3 (63) > \text{SbBr}_3 (29) > \text{TiBr}_4 (18) > \text{SnBr}_4 (0.9)$
 The values in parentheses are yields of p-methylacetophenone
- V. Isomerization of methylcyclopentane, alkylation of benzene, polymerization of styrene [53]
 $\text{AlBr}_3 > \text{GaBr}_3, \text{GaCl}_3 > \text{FeCl}_3 > \text{BCl}_3, \text{SnCl}_4, \text{SbCl}_3$
- VI. Friedel - Crafts benzoylation of aromatic compounds [54]
 Relative rate constants for $\text{K}_{\text{AlCl}_3} = 1$ in parentheses.
 $\text{FeCl}_3 (570) > \text{GaCl}_3 (500) > \text{AlCl}_3 (1) > \text{SnCl}_4 (0.003) > \text{BCl}_3 (0.0007)$.
- VII. Disproportionation of ethylmethylsilane [55]
 $(\text{AlBr}_3) > \text{AlCl}_3 > \text{GaBr}_3 > \text{BCl}_3 > \text{GaCl}_3, \text{SnCl}_4, \text{SbCl}_3$
- VIII. Polymerization of isobutylene [56]
 $\text{AlBr}_3 > \text{TiBr}_4 > \text{BBr}_3$
 $\text{TiCl}_4 > \text{BCl}_3 > \text{SnCl}_4$
- IX. Decomposition of benzazide [57]
 $\text{GaCl}_3 > \text{AlCl}_3 > \text{FeCl}_3 > \text{TiCl}_4 > \text{SnCl}_4 > \text{SbCl}_3$
- X. Conversion of camphene hydrochloride into isobornyl chloride [58]
 $\text{SnCl}_4 > \text{FeCl}_3 > \text{SbCl}_3$
- XI. Depolymerization of paraldehyde [59]
 $\text{BCl}_3 > \text{SnCl}_4 > \text{FeCl}_3 > \text{AlCl}_3 > \text{TiCl}_4$
- XII. Deuteroexchange during heterolysis of an alkyl halide [60]
 $\text{FeCl}_3 > \text{SnCl}_4$
- XIII. Reactions with indicators [61]
 $\text{AlCl}_3, \text{FeCl}_3 > \text{SnCl}_4, \text{SbCl}_3$
- XIV. Potentiometric titration of nitrogen bases in selenium oxychloride [62]
 $\text{FeCl}_3 > \text{SnCl}_4$
- XV. Ionization of triarylmethyl chloride [63]
 $\text{FeCl}_3 > \text{SnCl}_4 > \text{SbCl}_3$
- XVI. Shift of the notfully symmetrical pyridine vibration at 988 cm^{-1} during formation of molecular compound with a chloride [64]
 $\text{AlCl}_3 (32) > \text{SnCl}_4 (27) > \text{TiCl}_4 (25) > \text{SbCl}_3 (22)$
 Magnitude of shift (cm^{-1}) in parentheses.

Electrophilic substitution of hydrogen in aromatic compounds is the reaction most nearly related in mechanism to the acidic deuteroexchange reaction discussed in this paper [20-23]. This is illustrated by the broad similarity between the sequence of activities of halides reported in the literature for bromination, alkylation, and acylation of aromatic compounds. The strongest catalysts are the halides of aluminum and gallium, and these are followed by iron halides; less active are the halides of boron, titanium, trivalent antimony, and tin. An anomaly was observed for the Friedel-Crafts benzoylation of aromatic compound [54]. This was evidently due to the use as solvent of benzoyl chloride which forms molecular compounds with the most active chlorides. The stability of these molecular compounds increases with increasing strength of the chloride as a generalized acid.

SUMMARY

1. The following sequence of catalytic activity of bromides was established by the method of deuteroexchange between liquid deuterium bromide and benzene:



(Numbers in parentheses indicate approximately how much more quickly deuteroexchange proceeds with participation of the given bromide than with a solution of TiBr_4 of the same concentration.) SnBr_4 does not appreciably accelerate the reaction. InBr_3 is one of the strongest catalysts. Data obtained for the relative electrophilic characteristics of bromides are compared with literature data for their relative strength as generalized acids.

2. Catalysis of hydrogen exchange in aromatic compounds by acidlike bromides dissolved in liquid DBr is attributed to formation of complexes between aromatic compound, deuterium bromide, and bromide. It is assumed that the coordinative unsaturation of the bromide and the deuterium affinity of the hydrocarbon lead to polarization or rupture of the D-Br bond which favors entry of deuterium into the aromatic ring.

Formation of a compound between the functional group of an aromatic compound ($C_6H_5NO_2$, C_6H_5COOH) and a bromide suppresses the catalytic activity of the latter and inhibits hydrogen exchange in the aromatic ring.

3. The results are consistent with the theory that, depending on the experimental conditions, a hydrogen exchange reaction may proceed by an associative or an ionic mechanism, and that the two mechanisms may overlap. Existence of intermediate forms is also considered possible.

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THE REDUCING POWER OF SOME PENTOSES AND HEXOSES IN DEPENDENCE ON THEIR STRUCTURE. V

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The oxidation-reduction reaction between some sugars and potassium chromate in presence of sodium or potassium carbonate is accompanied by formation of a green compound of trivalent chromium [1]. This enabled the development of a micro method for determination of the sugar [2-5]. By means of this reaction we were able to detect differences in the reducing powers of some sugars [1].

In a closer study of the reducing properties of monosaccharides toward potassium chromate, and in connection with the development of micro methods for quantitative determination of sugars, we have been able to establish a relation between the reducing power of monosaccharides and their structure.

Earlier workers also noted a relation between the oxidative susceptibility of monosaccharides and their structure. Sugars substituted in the 2 position are weaker reducing agents than sugars with a free OH group in the 2 position [6]. On the basis of the work of a number of authors, Green [7] concluded that the influence on the oxidation of hexoses exerted by the *cis* position of the hydroxyl at the second carbon atom is greater than that of the hydroxyl at the first carbon atom.

In the present paper we submit results concerning the reducing power of some pentoses and hexoses in dependence on their structure.

EXPERIMENTAL

The reaction between oxidizing solution and sugar solution was carried out under the following conditions: Into a 100-ml conical flask were put 20 ml of 0.05 N $K_2Cr_2O_7$, 5 ml of 2 N Na_2CO_3 , and 10 ml of 0.05 M sugar solution. The reaction mixture was well stirred. The flask was closed with a stopper through which was inserted a 40-cm glass tube serving as an air condenser. The flask was then at once placed in a water bath with a temperature of $80 \pm 1^\circ$. The thermometer was secured to the flask in such a way that the mercury bulb was at the base of the flask. The temperatures of the flask contents and the bath water were equalized by continuous shaking of the flask contents and by stirring of the water in the bath with the flask in which the thermometer had been inserted.

The reducing power of the sugars was determined with heating of the oxidizing solution and the sugar for 5, 10, 20, 30, and 40 min. At the end of a heating period the flask was removed from the water bath and quickly cooled with running tapwater to room temperature. The condenser was then removed and 15 ml of 2 N H_2SO_4 was added to the reaction mixture, followed by about 0.5 g of KI. The flask was closed by a watch glass and allowed to stand in the dark for 5 min. The precipitated iodine was titrated with 0.5 N $Na_2S_2O_3$ in presence of starch.

At the start of the investigation a blank determination was carried out with solutions of $K_2Cr_2O_7$ and Na_2CO_3 under the experimental conditions with subsequent reduction of Cr^{6+} by potassium iodide in presence of H_2SO_4 .

We also ran experiments for determination of the reduction by a sugar of Cr^{6+} in presence of H_2SO_4 in the course of 5 min (i.e. for the period of reduction of excess of Cr^{6+} which had not reacted with the sugar during reaction of the sugar with chromate in presence of Na_2CO_3). Results of titration of the precipitated iodine with sodium thiosulfate indicated that the original quantity of Cr^{6+} was unchanged. The data below for reduction of Cr^{6+} consequently relate only to reaction of sugar with chromate in presence of Na_2CO_3 .

DISCUSSION OF RESULTS

Results obtained for the reducing power of D-glucose, D-galactose, D-mannose, D-xylose, L-arabinose, D-fructose, and D-sorbose are plotted in Figs. 1, 2, and 3. The reducing power of the sugars is expressed as the quantity of Cr^{6+} (in mg) reduced by 10 ml of 0.05 M solution of the sugar under the conditions described above.

The data obtained show that D-mannose has less reducing power than the other sugars investigated; D-sorbose, D-fructose, and D-xylose have the greatest.

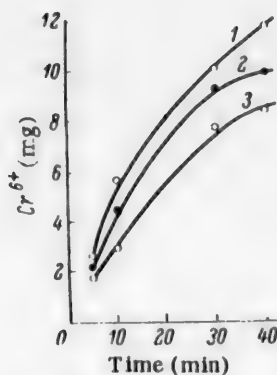


Fig. 1. Reducing power of D-glucose (1), D-galactose (2) and D-mannose (3).

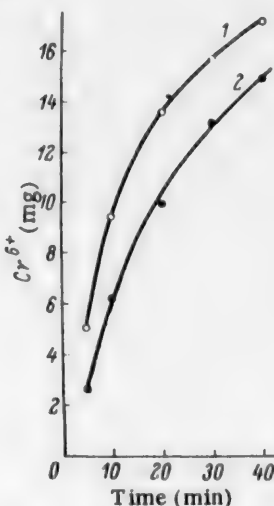


Fig. 2. Reducing power of D-xylose (1) and L-arabinose (2).

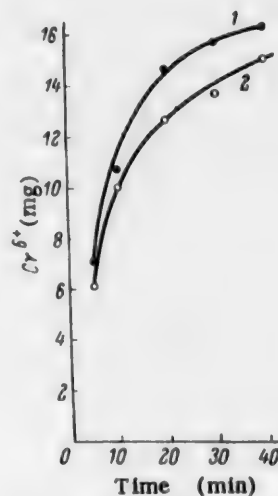


Fig. 3. Reducing power of D-sorbose (1) and D-fructose (2).

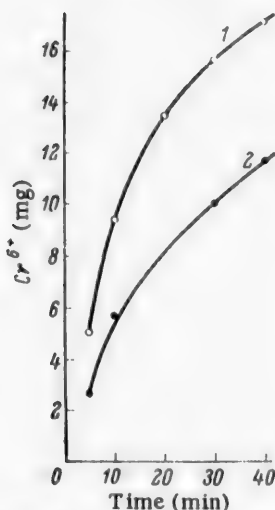


Fig. 4. Reducing power of D-xylose (1) and D-glucose (2).

Oxidation of the sugar by potassium chromate takes place in an alkaline medium. The content of oxo form in the solution, which has a higher chemical activity [8], therefore increases considerably. This is a reason for regarding the monosaccharides as being in the acyclic form when evaluating the results obtained.

According to Fig. 1 the reducing activity decreases in the sequence: D-glucose, D-galactose, D-mannose. On comparing the reducing power of the sugars in relation to their structure, we were struck by the fact that the number of hydrogen atoms directly linked to carbon on the right-hand side of the molecule and the distance of these hydrogens from the aldehyde group are correlated with the reducing power of the sugar. D-Glucose has only one hydrogen at C_3 . On the right-hand side of D-galactose is a hydrogen at C_4 in addition to one at C_3 . The reducing power of D-galactose is lower than that of D-glucose. D-Mannose is a weaker reducing agent than D-galactose although they have the same number of hydrogens in the right-hand carbons. This is because of the position of these hydrogens: On the right of D-mannose are hydrogens at C_3 and C_2 ; in D-galactose the hydrogens are at C_3 and C_4 . D-Galactose and D-mannose thus each have one hydrogen at C_3 on the right but the second hydrogen atoms are in different positions. The distance between the second right-hand hydrogen and the carbonyl group is smaller in D-mannose than in D-galactose, and this results in D-mannose being a weaker reducing agent.

We determined the reducing powers of two pentoses (D-xylose and L-arabinose) with the aim of checking our conclusion about the relation between reducing power of sugars and the number of hydrogens on the right-hand carbons and the distance of these hydrogens from the carbonyl group. On the right-hand side of the D-xylose molecule is one hydrogen at C_3 , while on the right-hand side of L-arabinose are two hydrogens at C_3 and C_4 . We therefore predicted that D-xylose must have a stronger reducing action than L-arabinose, and this was confirmed by experiment (see the curves of Fig. 2).

The relation between the reducing power of a sugar and its structure was also checked with the ketoses D-fructose and D-sorbose. D-Fructose contains a hydrogen on the right at C_3 and D-sorbose a hydrogen on the right at C_4 .

The hydrogen of D-fructose is nearer to the ketonic group than the hydrogen of D-sorbose. On the basis of the above rule we should expect D-sorbose to be a stronger reducing agent than D-fructose. This is confirmed by the curves of Fig. 3.

Our data indicate that the hydrogens of monosaccharides linked directly to carbon evidently influence the reducing activity of the sugar. The chemical bond between a carbon atom and a hydrogen atom in the carbon chain of a monosaccharide molecule is created by an electron pair displaced toward the carbon. This causes the hydrogen linked to the carbon to exert an influence on the oxidation of the aldehydic or ketonic group of the monosaccharide by inhibiting the process of its oxidation by an oxidizing solution. Without going more deeply into the cause of this dependence we wish to note in this connection that the hydrogens linked directly to carbon in a monosaccharide are not nonparticipants in the process of oxidation of the sugar, and the existence of this relation between reducing power of a monosaccharide and the location of the hydrogen atoms may be utilized for prediction of the relative reducing power of monosaccharides.

Comparison of the reducing powers of D-glucose and D-xylose (Fig. 4) and those of D-galactose and L-arabinose (Fig. 5) shows that pentoses are better reducing agents than the corresponding hexoses when the arrangement of the hydrogen atoms at the carbons is the same: D-xylose reduces more strongly than D-glucose, and L-arabinose more strongly than D-galactose. Consequently, shortening of the carbon chain of sugar molecules of identical structures leads to increasing reducing power.

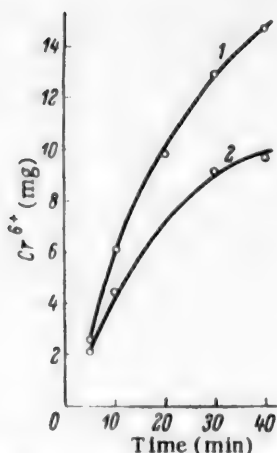


Fig. 5. Reducing power of L-arabinose (1) and D-galactose (2).

SUMMARY

1. Interaction of some pentoses and hexoses with potassium chromate in presence of sodium carbonate revealed a relation between one of the more important analytical properties of sugars—their reducing power—and their structure.
2. The reducing power of monosaccharides depends on the position of the hydrogen atoms on the right-hand side of the molecule. The reducing power of monosaccharides increases with increasing distance of these hydrogen atoms from the aldehyde or ketone group, with decrease in their number, and with decreasing length of the carbon chain.
3. By taking into account the position of the hydrogen atoms in a monosaccharide molecule directly linked to carbon, one can predict the relative reducing power of a sugar.

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THE CHEMISTRY OF 5-HALOFURANS

XV. REACTIONS OF HALOGEN REPLACEMENT IN 5-HALO-2-NITROFURANS

Z. N. Nazarova and V. N. Novikov

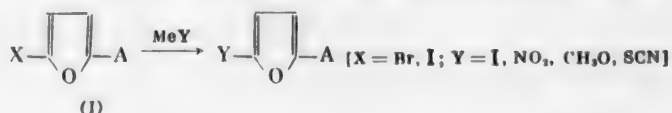
Rostov-on-Don State University

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 1,

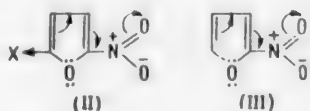
pp. 263-267, January, 1961

Original article submitted February 11, 1960

We earlier reported on the nucleophilic replacement of the halogen in 5-halo-2-substituted furans (I) by iodine [1-5], the nitro group [1,3,6], the methoxy group [7], and the thiocyno group [8-10].



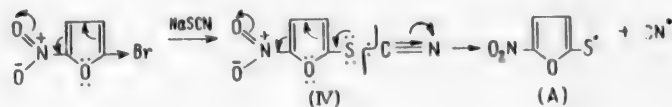
In the course of further study of replacement of the halogen in 5-halofurans (type I) we investigated the possibility of replacement of the halogen in 5-halo-2-nitrofurans (II) by iodine and nitro and thiocyno groups.



The nitro group is a strong acceptor; by creating $\delta+$ at the carbon atom in the 5 position in 2-nitrofuran (III) it facilitates nucleophilic attack, for example by the OH^- ion [11]; nitrofuran breaks down under the action of aqueous alkali. On the other hand the bromine atom in the 5 position of the furan ring causes the electron density to be slightly redistributed; it acts as an acceptor and facilitates $\delta+$ induction on the carbon atom to which it is linked. Consequently an attack by a nucleophilic reagent on the 5 position in 5-bromo-2-nitrofuran (II) ought to be realized with great facility. We confirmed this experimentally.

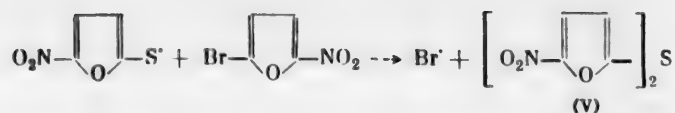
Halogen exchange ($\text{X} = \text{Br, I}$) in 5-halo-2-nitrofurans goes very easily when a mixture of halonitrofuran and alkali thiocyanate is boiled in acetone solution without a catalyst. Due to the good solubility of NaSCN in acetone and the insolubility of the precipitated NaBr , the kinetics of the reaction could be studied directly. We plotted the curve of separation of NaBr . The reaction is mainly completed in $\frac{1}{2}$ hour. The reaction gave not 5-thiocyno-2-nitrofuran (IV) but 5,5'-dinitrodifuryl-2,2'-sulfide* (V) (yield 90%).

We suggest that the first step in the reaction is nucleophilic replacement of bromine by the thiocyno group. Due to the electron-accepting influence of the NO_2 group, the intermediate thiocyno derivative is unstable and breaks down with formation of radicals (A) and CN^\bullet .



Radical (A) reacts with the molecule of 5-bromo-2-nitrofuran (II), displacing the Br^\bullet radical and forming sulfide (V):

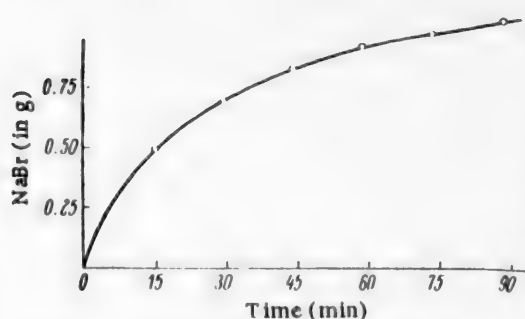
*5,5'-Dinitrodifuryl-2,2'-sulfide was obtained earlier in 71% yield by the action of thiourea on 5-bromo-2-nitrofuran [12].



The Br^\cdot and CN^\cdot radicals can give BrCN and later polythiocyanogen.



We isolated polythiocyanogen; the cyanogen ion was detected by passing CO_2 through the reaction mixture (diluted with water) and absorbing the liberated gases in alkali. Sodium bromide was separated nearly quantitatively from the reaction mixture; in the early course of the reaction the NaBr was white but toward the end of the reaction it was contaminated by yellow polythiocyanogen. Hardly any polythiocyanogen (but only white NaI) came down when a similar experiment was run with 5-iodo-2-nitrofur. This is evidently due to the compound ICN being inferior to BrCN as an oxidant.



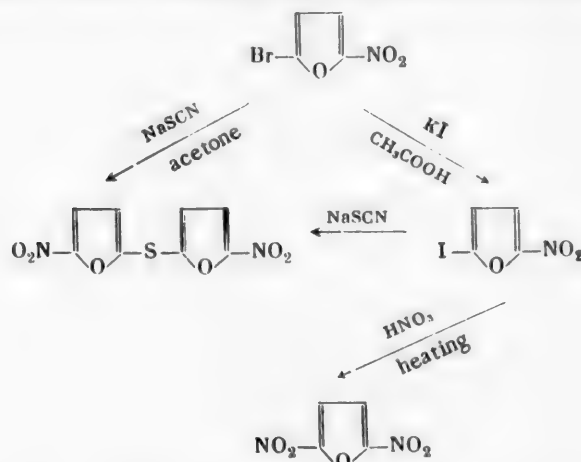
Curves of precipitation of NaBr in the reaction of 5-bromo-2-nitrofur with NaSCN in acetone.

5,5'-Dinitrodifuryl-2,2'-sulfide has a very high physiological activity; it inhibits the growth of staphylococci, and its synthesis by the new route may be of practical interest.

With the objective of comparing the mobility of the halogen in various 2-substituted 5-halofurans, we investigated the replacement of bromine by the thiocyno group under identical conditions for compounds of type (I) where $\text{A} = \text{NO}_2$, $\text{CH}=\text{CHNO}_2$, CHO ($\text{X} = \text{Br}$ or I). The reaction was performed in acetone or glacial acetic acid solution by boiling with metal thiocyanates [KSCN , NaSCN , $\text{Co}(\text{SCN})_2$, and $\text{Cu}(\text{SCN})_2$] (see table).

We see from the table that the ability of the halogen in 5-halo-2-substituted furans to exchange with other groups increases with increasing electronegativity of substituent A. This is also confirmed by experiments on nucleophilic replacement of bromine by iodine under the action of alkali metal iodides on compounds of type (I) in glacial acetic acid (see table). We established that the bromine in 5-bromo-2-nitrofur exchanges with iodine on boiling with KI in glacial acetic acid for a few minutes. The yield of 5-iodo-2-nitrofur* is nearly quantitative. The halogen (Br , I) in 5-halo-2-nitrofurans is very easily displaced by the nitro group when heated with conc. HNO_3 to give 2,5-dinitrofur. The latter was previously obtained [15] by direct nitration of furic acid followed by decarboxylation of the 5-nitro-2-furancarboxylic acid, as well as by decarboxylative nitration of 2,5-furandicarboxylic acid.

All of the transformations of 5-halo-2-nitrofurans can be summarized in the following scheme:



* 5-Iodo-2-nitrofur was earlier [13] prepared by the action of a solution of iodine in KI on the 5-mercurichloride derivative of 2-nitrofur. It was also prepared in low yield by treatment of 2,5-diiodofuran with HNO_3 [14].

Results of Reaction of Furan Derivatives $X-\text{C}_4\text{H}_3\text{O}-A$ with Salts MY

X	A	Y	Me	Solvent	Cat- alyst	Reaction temper- ature	Reaction duration (hr)	Reaction product	Yield (%)	Melting point
Br I	NO ₂	SCN	Na K	Acetone Acetic acid	—	50—60° 100—120	0.5—1 0.5	[O ₂ N—C ₄ H ₂ O—] ₂ S (V) [O ₂ N—C ₄ H ₂ O—] ₂ S (V)	90 69.4	98—99° 97—98
Br I	CH=CHNO ₂	SCN	Na K	Acetone Acetic acid	Co ⁺⁺ , Cu ⁺⁺ light	50—60 100—120	1—2 2	NCS·C ₄ H ₂ O—CH=CHNO ₂ • HOOCSC—C ₄ H ₂ OCH=CHNO ₂	85 60	74.5 147—148
Br I	CHO	SCN	K Na	Acetone Acetic acid	Co ⁺⁺ , Cu ⁺⁺ light	50—60 70	6 40	No exchange HOOCSC—C ₄ H ₂ O—CHO	— 60	— 127
Br	NO ₂	I	Na K	Acetic acid	—	100—120	Several minutes	I—C ₄ H ₂ O—NO ₂	98	76
Br	CH=CHNO ₂	I	Na K	Acetic acid	light	100—120	2	I—C ₄ H ₂ O—CH=CHNO ₂	85	113—114
Br	CHO	I	Na K	•	light	100—120	2	I—C ₄ H ₂ O—CHO	95	127—128
Br	CH=CHCOOC ₂ H ₅	I	Na K	•	Co ⁺⁺ , Cu ⁺⁺ light	100—120	0.5—1	I—C ₄ H ₂ O—CH=CHCOOH	55	168
Br	COOC ₂ H ₅	I	Na K	•	Cu ⁺⁺ light	100—120	3—4	Br—C ₄ H ₂ O—COOH	80	184—185

• We previously obtained this in 74% yield [9].

EXPERIMENTAL

5-Bromo-2-nitrofuran. To 25 ml of acetic anhydride was added dropwise 25 ml of conc. HNO_3 (d 1.5) with strong cooling (-10°) and mechanical stirring. A solution of 6 g of 5-bromofuroic acid [16] in 25 ml of acetic anhydride (prepared by dissolution in small portions of finely pulverized acid in hot acetic anhydride) was then added dropwise at -10° and with vigorous stirring. During the latter operation the acid must not crystallize from the solution. After the whole of the 5-bromofuroic acid had been added to the reaction mixture (2-3 hr), the mixture was stirred for another hour, and then addition was made of a further 6 ml of conc. HNO_3 and the mixture again stirred for 30 min, after which it was poured onto ice and extracted five times with ether. The ethereal extract was distilled with steam. After the ether had distilled, 5-bromonitrofuran came over with the steam and crystallized in the condenser; m.p. 48° [15]. Yield 2.8 g (47%). 5-Bromonitrofuran has a strong burning action on the skin in vanishingly small concentrations.

5-Iodo-2-nitrofuran. A mixture of 1.92 g of 5-bromo-2-nitrofuran (BNF), 1.82 g of KI, and 30 ml of glacial acetic acid was refluxed for 20-25 min. The mass was then poured into water and left overnight in a refrigerator. Lustrous crystals of 5-iodo-2-nitrofuran came down; m.p. 76° [13,14]. Yield 2 g (85%). A further 0.3 g (13%) of 5-iodo-2-nitrofuran could be separated from the mother liquor.

2,5-Dinitrofuran. A mixture of 1 g of 5-iodo-2-nitrofuran and 30 ml of conc. HNO_3 (d 1.34) was heated; at the boiling point iodine vapor started to come off violently. The mixture was boiled until the iodine vapor had been removed (2-3 min); active carbon was added and the mixture filtered hot; the cooled filtrate deposited lustrous crystals of 2,5-dinitrofuran with m.p. 100° [11]. 2,5-Dinitrofuran is readily soluble in water, and its yield can be increased by several extractions of the mother liquor with ether. Lustrous, white crystals with m.p. $99-100^\circ$ (from aqueous methanol). Total yield 0.5 g (75.3%). 2,5-Dinitrofuran is similarly formed from 5-bromo-2-nitrofuran in 85% yield.

5,5'-Dinitrodifuryl-2,2'-sulfide (V). A mixture of 1.92 g of BNF, 1.62 g of anhydrous NaSCN, and 30 ml of anhydrous acetone was boiled on a water bath for 2 hr. The mixture was filtered, and the filtrate poured into water and left overnight. Lustrous coffee-colored leaflets came down on standing. The precipitate was collected, washed with cold water, recrystallized from methanol (+ carbon), and dried in a desiccator over P_2O_5 . Nearly white crystals with m.p. $98-99^\circ$. Yield 1.3 g (90%).

Found %: N 10.76, 10.86. $\text{C}_8\text{H}_6\text{O}_6\text{N}_2\text{S}$. Calculated %: N 10.94.

b) A mixture of 1.92 g of BNF, 1.94 g of KSCN, and 30 ml of glacial acetic acid was heated for an hour on a boiling water bath. The precipitated polythiocyanogen was suction filtered, and the filtrate was poured into water and left overnight. Brown crystals came down and were recrystallized from methanol (+ carbon) to give 1 g (69.4%) of yellowish crystals with m.p. $97-98^\circ$. A mixture with 5,5'-dinitrodifuryl-2,2'-sulfide melted at $97-98^\circ$.

c) A mixture of 2.39 g of 5-iodo-2-nitrofuran, 1.62 g of NaSCN, and 40 ml of acetone was heated for 6 hr on a water bath. There was obtained 1.16 g (80.3%) of (V) with m.p. $98-99^\circ$ (from methanol). A mixture with 5,5'-dinitrodifuryl-2,2'-sulfide melted at 98° .

The same result was obtained on reaction of 5-iodo-2-nitrofuran with sodium thiocyanate in nitromethane.

SUMMARY

1. It was shown that the halogen in 5-halo-2-nitrofurans easily enters into exchange reaction with MI, MSCN, and nitric acid.

2. New methods are proposed for synthesis of 5,5'-dinitrodifuryl-2,2'-sulfide, 5-iodo-2-nitrofuran, and 2,5-dinitrofuran.

3. A mechanism is advanced for the formation of 5,5'-dinitrodifuryl-2,2'-sulfide from 5-halo-2-nitrofurans and MSCN.

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BREAKDOWN OF ACYL PEROXIDES IN ACIDS

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Reports of the possibility of regenerative exchange in a carboxylic acid medium have been published [1,2].



Experimental proof of this, however, is lacking. On breakdown of acetyl peroxide in labeled acetic acid $C^{14}H_3COOH$ it was shown that such an exchange is very insignificant if it takes place at all (approximately 1%) [3]. It may be explained in terms of the exothermic decomposition of $RCOO\cdot$ radicals into R and CO_2 [4]. Thermal effects of 17, 14, and 13 kcal were found respectively for $R = CH_3$, C_2H_5 , and C_3H_7 . Consequently the decarboxylation of the $CH_3COO\cdot$ radical proceeds nearly simultaneously with dissociation of the oxygen-oxygen bond of the peroxide. On the other hand the breakdown of the benzoyloxy radical is a thermally neutral process. Hence $C_6H_5COO\cdot$ can have a longer life and there is a greater probability of its exchange with solvents. This has been experimentally confirmed [5]. Thus the decomposition of benzoyl peroxide in acetic and propionic acids led to formation of methane or ethane among the reaction products. Methane or fluoroform were not found in similar reactions of propionyl peroxide in acetic or trifluoroacetic acids. The authors [5] conclude that the ethyl radicals formed on decarboxylation of the unstable $C_2H_5COO\cdot$ radical are incapable of abstracting the carboxylic hydrogen of the acid. In the case of benzoyl peroxide 3-7% of the peroxide radicals attack the $RCOO-H$ bond of the acid. However it has not been established which of the two possible radicals— $C_6H_5COO\cdot$ or $C_6H_5\cdot$ —abstracts the hydrogen. The authors think that formation of a hydrogen bond between the stable $C_6H_5COO\cdot$ radical and the carboxyl of the solvent is more probable.

We were interested in making yet another attempt to establish the "estafette" transfer of acyloxy radicals (1) in a carboxylic acid medium. We made use of the reaction of more stable (compared to the acetyloxy radical) benzoyloxy and m-nitrobenzoyloxy radicals in a medium of acetic and benzoic acids labeled in the carboxyl with C^{14} . Separation of labeled $C^{14}O_2$ could be considered evidence of the occurrence of such an exchange if the original acids and the products formed do not split off CO_2 during the reaction. Spontaneous decarboxylation of acetic and benzoic acids at 100° is excluded. In regard to the reaction products, the literature contains a great deal of data on the decomposition of acyl peroxides in acids and their derivatives.

Decomposition of benzoyl peroxide in acetic acid gives CO_2 , benzene, diphenyl, and benzoic, p-phenylbenzoic, homophthalic, and homoterephthalic acids [6]. Decomposition of acetylbenzoyl peroxide in acetic acid gives CO_2 , methane, benzene, methyl benzoate, diphenyl, and benzoic, succinic, and homophthalic acids [7]. Reaction of m-nitrobenzoyl peroxide with fused benzoic acid leads to formation of 3-nitrophenyl-3'- and -4'-carboxylic acids [8]. In addition small quantities of nitrobenzene and 3,3'-dinitrodiphenyl were isolated. Nothing appears to have been published, however, about the products of reactions of benzoyl peroxide and acetylbenzoyl peroxide in benzoic acid, or of m-nitrobenzoyl peroxide in acetic acid. We therefore decided in the first place to determine the main products of these reactions.

Experiments on the decomposition of acetylbenzoyl peroxide in benzoic acid at 90° led to formation of CO_2 , methyl benzoate, and a mixture of phenylbenzoic acids. Other products containing the phenyl group (benzene or diphenyl) were not found. Decomposition of benzoyl peroxide in benzoic acid at 90° gave CO_2 , a mixture of phenylbenzoic acids, and small quantities of diphenyl and phenyl benzoate. Benzene was not detected. Breakdown of m-nitrobenzoyl peroxide in glacial acetic acid led to formation of CO_2 , nitrobenzene, m-nitrobenzoic acid, and a large quantity of nitrogen-containing higher aromatic acids.

TABLE 1. Decomposition of Acyl Peroxides in Acids Labeled with C^{14} in the Carboxyl*

Expt. no.	Taken into reaction				Reaction conditions			BaCO ₃ isolated		Relative activity d : c (%)
	peroxide		acid		molar ratio a : b	temperature (hr)	duration (hr)	activity (in mole)	activity (pulses/min)	
	name	quantity (in mole) (a)	name	quantity (in mole) (b)						
1	Acetylbenzoyl	0.0055	Benzoic	0.041	38780	1 : 7.5	90 ^a	0.007	6010	2.2
2	Acetylbenzoyl	0.0055	Benzoic	0.137	4420	1 : 25	90	0.0065	1640	5.3
3	Acetylbenzoyl	0.0055	Benzoic	0.237	4700	1 : 50	90	0.006	2100	6.4
4	Acetylbenzoyl	0.011	Acetic	1.65	27690	1 : 150	90	0.012	2360	4.3
5	Acetylbenzoyl	0.010	Acetic	1.50	5910	1 : 150	90	0.0065	540	4.5
6	Benzoyl	0.004	Benzoic	0.041	7285	1 : 10	90	0.0033	1200	2.3
7	m-Nitrobenzoyl	0.008	Acetic	1.20	6520	1 : 150	90	0.005	2764	21.2
8	m-Nitrobenzoyl	0.045	Acetic	7.08	6530	1 : 150	70	0.006	3100	24.6
9	m-Nitrobenzoyl	0.005	Benzoic	0.050	7280	1 : 10	100	0.0035	6413	12.6

* Similar results of parallel experiments are given in the table.

** The peroxide decomposed incompletely.

Experiments on decomposition of benzoyl peroxide, acetylbenzoyl peroxide, and m-nitrobenzoyl peroxide in $C_6H_5C^{14}OOH$ and $CH_3C^{14}OOH$ revealed that 2-25% of the total CO_2 formed was $C^{14}O_2$. Decomposition was performed at 70-100° (in the case of benzoic acid the components sintered at this temperature). Results are set forth in Table 1 which shows that the $C^{14}O_2$ activity (determined on $BaC^{14}O_3$) is 2.2-2.3% for the reaction of benzoyl peroxide and acetylbenzoyl peroxide in benzoic acid (Table 1, Expts. 1 and 6).

With increasing molar ratio of peroxide to acid (a:b = 1:7.5 to 1:50) the CO_2 activity rises to 6.4% (Expts. 1, 2, and 3). The activity increase is especially conspicuous in the decomposition of m-nitrobenzoyl peroxide in benzoic and acetic acids—12.6 and 21.2% respectively (Expts. 7 and 9). The activity rises to 24.6% with fall in reaction temperature to 70°.

These data coupled with the earlier analyses of the reaction products led us to the conclusion that the only possible source of the $C^{14}O_2$ is the decarboxylation of the $RC^{14}OO\cdot$ radicals of the labeled solvent.

It should be noted that acetylbenzoyl peroxide differs from other peroxides in giving a considerable amount of methyl benzoate when decomposed in acids, especially in presence of benzoic acid (about 70%). The ester may have been formed by molecular breakdown



or by initiated decomposition



The high yield of methyl benzoate on reaction of peroxide in benzoic acid is more likely to result from reaction (2). In such a case the quantity of peroxide breaking down with formation of free radicals is 1/3 of the total utilized. This very greatly alters the $C^{14}O_2/CO_2$ total ratio, where CO_2 total includes only free-radical decomposition. The corresponding calculation of the $C^{14}O_2$ activity in this case (Table 1, Expt. 1) increases its quantity to 8%. Ester formation was negligible in the other reaction and such a calculation would not appreciably alter the results set forth.

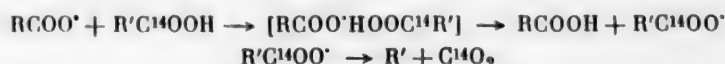
Formation of the $R'COO\cdot$ radical from acid is possibly due to removal of carboxylic hydrogen both by $RCOO\cdot$ and by the R radical of the peroxide. The latter, however, is less probable in the light of Kharasch's data for dehydrogenation of alcohols by the R radical of a peroxide [9]. We were interested in establishing the possibility of these reactions in our case. With this objective we made use of acetic acid deuterated in the carboxyl group. From the isotopic composition of the resulting RH we can quantitatively evaluate the dehydrogenation of the carboxyl by the R radical. It was not possible to directly determine the deuterium content in $RCOOD$ formed by the peroxide radical according to reaction (1) due to the rapid exchange of the carboxylic hydrogens of the acids.

TABLE 2. Decomposition of Acyl Peroxides in Acetic Acid at 90° with a 1:150 Molar Ratio

Peroxide	Isolated		Isotopic composition		Quantity of labeled substances (in mole)
	substances	moles per mole peroxide	Activity (in % of original $\text{CH}_3\text{C}^{14}\text{OOH}$)	Deuterium content (in % of original CH_3COOD)	
Benzoyl	CO_2	1.3	4.5	—	0.0585
	C_6H_6	0.62	—	3.0	0.0186
m-Nitrobenzoyl	CO_2	1.08	21.2	—	0.229
	$\text{C}_6\text{H}_5\text{NO}_2$	0.2	—	1.2	0.0024

Results of experiments on decomposition of benzoyl peroxide and m-nitrobenzoyl peroxide in CH_3COOD are set forth in Table 2, which shows that in the case of the phenyl radical the deuterium removal amounts to 3%, while in the case of the nitrophenyl radical it amounts to 1.2%. The quantity of labeled C^{14}O_2 is far from being balanced by the deuterated benzene or nitrobenzene. In the case of m-nitrobenzoyl peroxide the $\text{C}_6\text{H}_5\text{DNO}_2/\text{C}^{14}\text{O}_2$ ratio is only 1%.

Consequently the acyloxy radical of the peroxide is mainly responsible for the abstraction of the carboxylic hydrogen of the acid. We call this process "estafette" radical transfer.



A similar reaction of the phenyl radical in benzene as solvent was previously described [10]. The greater facility of carboxylic hydrogen abstraction by the RCOO^\bullet radical is in harmony with views on the possibility of formation of a hydrogen bond between an acyloxy radical and acid [5]. The resulting $\text{R}'\text{C}^{14}\text{OO}^\bullet$ is decarboxylated to give labeled C^{14}O_2 . Estafette transfer is more conspicuous at low concentrations of peroxide (Table 1, Expts. 2 and 3). This process is more conveniently observed in the case of displacement of the less stable $\text{CH}_3\text{C}^{14}\text{OO}^\bullet$ by the more stable $\text{C}_6\text{H}_5\text{COO}^\bullet$ or $\text{O}_2\text{NC}_6\text{H}_4\text{COO}^\bullet$ radical. Thus in the decomposition of benzoyl peroxide and m-nitrobenzoyl peroxide in acetic acid (Table 1, Expts. 5 and 7) the C^{14}O_2 activity increases because the decarboxylation of stable $\text{C}_6\text{H}_5\text{COO}^\bullet$ or $\text{O}_2\text{NC}_6\text{H}_4\text{COO}^\bullet$ radicals is on a smaller scale than the displacement by them of the unstable $\text{CH}_3\text{C}^{14}\text{OO}^\bullet$ [11]. This is also illustrated by the breakdown of m-nitrobenzoyl peroxide in benzoic and acetic acids (Table 1, Expts. 7 and 9). With falling reaction temperature the CO_2 activity also rises because at lower temperatures the difference between the stabilities of $\text{CH}_3\text{COO}^\bullet$ and m- $\text{O}_2\text{NC}_6\text{H}_4\text{COO}^\bullet$ radicals is still more pronounced. Our results are in accord with literature data on the breakdown of benzoyl peroxide in acetic acid: Our value of $\text{C}^{14}\text{O}_2/\text{CO}_2$ total = 0.046 for breakdown of benzoyl peroxide in acetic acid agrees with the value of $\text{CH}_4/\text{CO}_2 = 0.044-0.031$ [4].

The authors thank S. F. Zhil'tsov for carrying out the radiometric measurements.

EXPERIMENTAL

Reaction of acetylbenzoyl peroxide with benzoic acid. Numerous attempts to perform the reaction in fused benzoic acid were always accompanied by explosions. We therefore decided to operate at the sintering temperature of the components (90-100°). Under these conditions the reaction went fairly quietly, and comparable results were obtained in parallel experiments.

A solution in ether was prepared at low temperature from 3.0 g of acetylbenzoyl peroxide (0.017 mole) and 10 g of benzoic acid (0.082 mole). This procedure ensured better mixing of the components. The ether was then taken off. The mixture of components (1:5 molar ratio) was heated at 90° for 6 hr. During the reaction 0.7 g of CO_2 (0.016 mole) came off. The reaction mixture was neutralized with sodium carbonate. The neutral products were distilled with steam. There was isolated 1.6 g (0.012 mole) of methyl benzoate with b.p. 195°. Benzene was not detected. Acidification of the solution of salts yielded a mixture of acids. A qualitative test for acetic acid with As_2O_3 was negative. Benzoic acid was isolated from the mixture by numerous washings with hot water and by distillation with steam. The residue (0.92 g), insoluble in hot water, was a mixture of substituted benzoic acids. Sublimation in

vacuo yielded p-phenylbenzoic acid with m.p. 223°; a mixture with authentic and pure p-phenylbenzoic acid melted at 225°. The acid equivalent was found to be 193 (theoretical value 198). o-Phthalic acid was detected in the acid products by the resorcinol test.

Reaction of benzoyl peroxide with benzoic acid. A mixture of 5.0 g (0.0207 mole) of benzoyl peroxide and 15.0 g (0.123 mole) of benzoic acid (1:6 molar ratio) was heated at 100-110° for 10 hr. This treatment led to evolution of 0.75 g of CO₂ (0.017 mole). A trap filled with active carbon and cooled to -80° was provided for collection of the expected benzene. After completion of the reaction, the contents of the trap were quickly subjected to distillation with steam. No nitro derivative was detected after extraction of the distillate with CCl₄ and nitration with extreme caution. The reaction mixture was worked up as in the preceding experiment. Steam distillation of the neutralized residue gave 0.31 g of a mixture of biphenyl and phenyl benzoate. The ester content (determined by saponification) was 0.0017 mole. Fractional crystallization of the acid products (after removal of the benzoic acid) gave 2.34 g of a mixture of acids from which by sublimation was isolated p-phenylbenzoic acid with m.p. 225° (no depression in admixture with an authentic specimen). In addition 5.78 g of a mixture of benzoic and phenylbenzoic acids was isolated. Determination of the acid equivalent gave a content of 16% phenylbenzoic acids in this mixture. A total of 0.016 mole of phenylbenzoic acids was found. The residue from the steam distillation contained 0.29 g of resin.

Reaction of m-nitrobenzoyl peroxide with acetic acid. A mixture of 24.8 g (0.74 mole) of m-nitrobenzoyl peroxide and 245 g (~ 4 moles) of glacial acetic acid (1:54 molar ratio) was heated at 90° for 20 hr with loss of 3.55 g (0.080 mole) of CO₂. The reaction products were analyzed as follows. The main bulk of acetic acid was distilled off, using a dephlegmator. Steam distillation of the neutralized residue gave 2 g of nitrobenzene. The steam distillate was extracted with CCl₄ and nitrated. We obtained 2.48 g (0.015 mole) of m-dinitrobenzene, m.p. 88°. Fractional crystallization of the solution of acids yielded 5.6 g (0.034 mole) of m-nitrobenzoic acid, m.p. 132° (no depression in admixture with an authentic specimen). We also isolated 10 g of nitrogen-containing higher acids.

Reaction of m-nitrobenzoyl peroxide with CH₃COOD. m-Nitrobenzoyl peroxide (15 g or 0.044 mole) was decomposed in 150 ml of CH₃COOD (96300 γ of deuterium in the carboxyl) by heating at 90° for 15 hr. The solvent was distilled and the residue neutralized with sodium carbonate and distilled with steam. Nitrobenzene separated in the form of heavy, oily drops and was collected and nitrated to m-dinitrobenzene. There was obtained 1.54 g of m-dinitrobenzene with m.p. 88° (no depression of melting point in admixture with an authentic specimen). In the water of combustion of the m-dinitrobenzene was found 285 γ of deuterium (1140 γ per atom of hydrogen in the m-dinitrobenzene).

Reaction of benzoyl peroxide with CH₃COOD. Benzoyl peroxide (12.1 g or 0.050 mole) in 392 ml of CH₃COOD (about 100,000 γ of deuterium in the carboxyl) was heated at 90° for 5 hr with loss of 2.86 g (0.065 mole) of CO₂. Only benzene was isolated from the reaction product. Nitration gave 5.21 g (0.031 mole) of m-dinitrobenzene with m.p. 89°. In the water of combustion of the m-dinitrobenzene was found 772 γ of deuterium (3088 γ per hydrogen atom of the m-dinitrobenzene).

Reactions of acyl peroxides in carboxylic acids labeled with C¹⁴ in the carboxyl. Reactions were carried out in a two-necked, round-bottomed flask connected to a bulb condenser with four traps and a tube for admission of purified nitrogen. A weighed sample of the acyl peroxide in RC¹⁴OOH was heated in a nitrogen stream on a water or glycerol bath. The gaseous products of reaction passed through reflux condenser, two traps cooled to -80°, and then through two traps containing Ba(OH)₂ solution. In the first two traps the CO₂ was freed of acid vapors, and in the second pair of traps it was bound as BaCO₃. After completion of the reaction, the BaCO₃ was filtered, dried, and analyzed for its C¹⁴ content. The complete absence of traces of active acids from the separated CO₂ was checked in blank experiments carried out under similar conditions. A weighed sample of active acid was heated at 90° in a dry nitrogen stream. An equivalent quantity of ordinary BaCO₃ had previously been put into the barytes water trap. After 5- to 6-hr heating in the nitrogen stream, the BaCO₃ was filtered and analyzed for its C¹⁴ content. Results of blank experiments run with active acetic (1.5·10¹⁴ pulses/min) and benzoic (7·10¹⁴ pulses/min) acids showed that the BaCO₃ was substantially free of activity (50 and 30 pulses/min respectively).

Isotopic composition of the substances. The waters of combustion were analyzed for deuterium by the flotation method. Measurements were accurate to 30 γ.

Radiometric analysis for the C¹⁴ content was carried out in an internally filled counter. The counter mixture consisted of n-hexane vapor and the CO₂ being analyzed, which was obtained by burning the substance or by decom-

position of BaCO_3 with mineral acid. The relative activity of radiocarbon C^{14} is given in the paper. Measurements were made with an MS-4 counter tube with a volume of 29.95 ml at a pressure of the CO_2 sample of 40 mm mercury column. This is equivalent to 1.44 ml of CO_2 under normal conditions.

SUMMARY

1. The decomposition of benzoyl, acetylbenzoyl, and m-nitrobenzoyl peroxides in acetic and benzoic acids labeled with radiocarbon C^{14} in the carboxyl was investigated. It was shown that the liberated carbon dioxide contains between 2 and 25% of active C^{14}O_2 .

2. Decomposition of benzoyl peroxide and m-nitrobenzoyl peroxide was effected in deuterioacetic acid CH_3COOD . It was found that the R radical of the peroxides abstracts between 1 and 3% of the deuterium from the carboxyl of the acid ($\text{R} = \text{C}_6\text{H}_5$, $\text{C}_6\text{H}_4\text{NO}_2$).

3. Separation of labeled C^{14}O_2 is attributed to estafette transfer of acyloxy radicals with the carboxylic acid.

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STUDY OF THE THERMAL DECOMPOSITION OF ACETYLCYCLOHEXANESULFONYL PEROXIDE IN VARIOUS SOLVENTS

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Great interest is attached to the acetylcyclohexanesulfonyl peroxide synthesized by Graf. It has found application in several reactions proceeding by a radical mechanism [1-4]. Decomposition of the peroxide was only carried out in cyclohexane [1]. It appeared of interest to us to study reactions of this peroxide in which homolytic breakdown gives two different radicals: cyclo- $C_6H_{11}SO_2O\cdot$ and $CH_3COO\cdot$. This would enable comparison of their properties and would throw fresh light on the mechanism of the reaction of acyl peroxides.

For study of thermal decomposition of the peroxide we chose both hydrogen-containing organic solvents differing in their ability to supply hydrogen atoms to the free radicals of the peroxide and saturated halogenated solvents. Kinetic investigations were made in isopropyl alcohol, cyclohexane, benzene, and carbon tetrachloride. Decomposition was found to follow a first-order law (Figs. 1-4) [5]. The apparent energies of activation in the solvents were calculated from the slope of the straight-line plots (Fig. 5) (see Table 1).

TABLE 1. Calculated Rate Constants of Decomposition and Apparent Activation Energies

Temperature	Rate constant $k \times 10^5 \text{ sec}^{-1}$			
	isopropyl alcohol	cyclohexane	C_6H_6	CCl_4
18°	5.12	—	—	—
20	13.90	9.59	—	—
25	30.20	15.54	—	—
30	50.20	34.50	—	—
35	—	—	5.76	—
40	—	127.90	11.30	4.15
45	—	—	21.55	7.02
50	—	—	—	16.45
55	—	—	74.00	29.70
E (kcal/mole)	25.5	23.4	25.6	26.8

The results show that the rate of decomposition of acetylcyclohexanesulfonyl peroxide in different solvents falls in the following sequence: isopropyl alcohol > cyclohexane > benzene > carbon tetrachloride.

It is noteworthy that the different solvents have similar activation energies.

Reaction of the peroxide with the above solvents yielded cyclohexanesulfonic acid, cyclohexenesulfonic acid, acetic acid, methane, methyl chloride, carbon dioxide, methyl and cyclohexyl esters of cyclohexanesulfonic acid, hexachloroethane, acetone, and cyclohexene (Table 2).

We see from Table 2 that reaction with the solvents always gives a mixture of sulfonic acids whose quantity increases from 0.6 mole in cyclohexane to 0.9 mole in carbon tetrachloride. It follows that sulfonic acids can be

TABLE 2. Decomposition of Acetylcyclohexanesulfonyl Peroxide in Various Solvents (Initial Concentration $C_0 = 0.7$ M)

Products Isolated (mole/mole peroxide)	Solvents			
	iso- C_3H_7OH (20°)	cyclo- C_6H_{11} (35°)	C_6H_6 (50.4°)	CCl_4 (55.4°)
CH_4	0.64	0.62	0.28	—
CO_2	0.95	0.96	0.54	0.93
$C_6H_{11}SO_3H$	0.72	0.53	0.59	0.58
$C_6H_5SO_3H$	0.02	0.08	0.27	0.32
$C_6H_{11}SO_3OCH_3$	0.26	} 0.40 * {	0.20	0.17
$C_6H_{11}SO_3OC_6H_{11}$	—		—	—
CH_3COCH_3	0.57		—	—
CH_3COOH	0.02	—	0.34	—
C_6H_{10}	—	0.067	—	—
CH_2Cl	—	—	—	0.62
C_2Cl_6	—	—	—	0.24
HCl	—	—	—	0.08
Resin:	—	—	10 **	traces

* Mixture of methyl and cyclohexyl cyclohexanesulfonates.

** In percent of weight of peroxide.

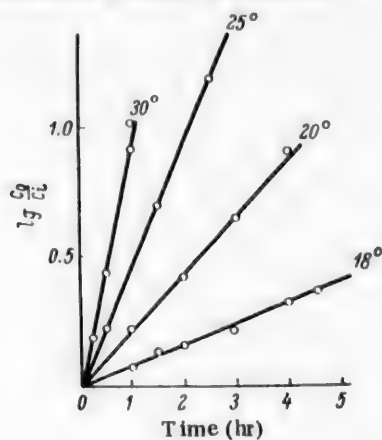


Fig. 1. Decomposition of 0.1 M peroxide solution in iso- CH_3CH_2OH .

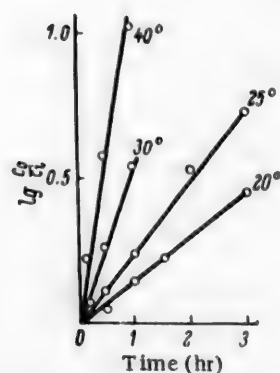


Fig. 2. Decomposition of 0.1 M peroxide solution in cyclohexane.

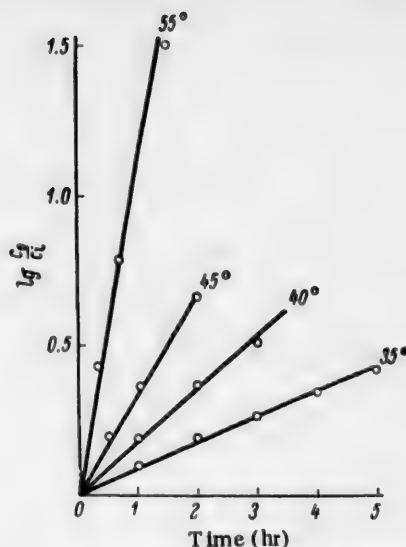


Fig. 3. Decomposition of 0.1 M peroxide solution in benzene.

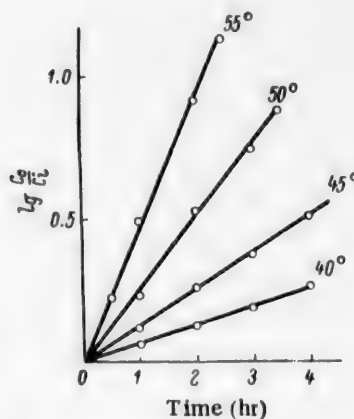


Fig. 4. Decomposition of 0.1 M peroxide solution in CCl_4 .

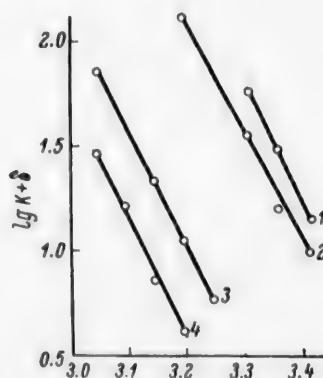


Fig. 5. Rate of decomposition of peroxide as a function of the temperature. The straight lines 1 to 4 correspond to reactions in isopropyl alcohol, cyclohexane, benzene, benzene, and CCl_4 .

formed both by reaction of the $C_6H_{11}SO_2O^\bullet$ radical with hydrogen-containing solvents and by reaction of dissolved peroxide molecules with radicals or by disproportionation of the latter (this occurs in carbon tetrachloride). In the light of these facts we should expect the quantity of unsaturated sulfonic acid to increase in the sequence: isopropyl alcohol < cyclohexane < benzene < carbon tetrachloride. This was confirmed by experiments. The yield of unsaturated sulfonic acid depends on the temperature. In the reaction of acetylcyclohexanesulfonyl peroxide with isopropyl alcohol the quantity of cyclohexenesulfonic acid increases from 2.5 at 20° to 8.0% at 35°.

The reaction products always include the methyl ester of cyclohexanesulfonic acid in a quantity that hardly changes with changing concentration of peroxide (Table 3). It is probably therefore formed by molecular decomposition of the initial peroxide or by "cage" reaction of the solvent. In this case induced decomposition appears to play a secondary role. The cyclohexyl ester of cyclohexanesulfonic acid is possibly formed by exchange interaction of peroxide with cyclohexane.

Carbon dioxide is nearly quantitatively evolved in the reaction of the peroxide with isopropyl alcohol, cyclohexane, and carbon tetrachloride. We did not, however, observe an equimolar ratio of CO_2 to $CH_4(CH_2Cl)$, which was found in the reaction of acetylbenzoyl peroxide with alcohols [6]. This inequality of volumes is further evidence in favor of molecular decomposition of the initial peroxide with formation of an ester. Separation of a very small amount of acetic acid during decomposition of the peroxide in isopropyl alcohol also shows the difference in behavior of these two peroxides. In the case of acetylcyclohexanesulfonyl peroxide the CO_2/CH_3COOH ratio is 47.5 at 20° and the molar peroxide: solvent ratio is 1:19; in the case of acetylbenzoyl peroxide the respective ratios are 4.8 at 82° and 1:23.

A set of experiments, in which the reaction temperature and the peroxide concentration were varied, was carried out with the aim of clarifying the mechanism of the reaction of the peroxide with isopropyl alcohol. The methyl ester was determined by saponification followed by oxidation of the methyl alcohol in the distillate. However, the dimedon derivative of formaldehyde could not be obtained. Acetone 2,4-dinitrophenylhydrazone (m.p. 124°) was isolated. This indicated the presence of isopropyl alcohol. Since in the series of experiments there was a considerable difference between the CH_4 and CO_2 yields, we made a study of decomposition of peroxide labeled with C^{14} in the CH_3 group in isopropyl alcohol. Methyl alcohol was detected in the distillate of the solvent by radiometric analysis**. This alcohol is formed by alcoholysis of the ester and comes over with the isopropyl alcohol. A material balance of the reaction products was carried out at the same time (Table 4).

TABLE 3. Relation Between Yield of Methyl Ester of Cyclohexanesulfonic Acid in the Reaction Products and the Peroxide Concentration in Different Solvents

Products isolated (mole/ mole peroxide)	Solvents					
	iso- C_3H_7OH		cyclo- C_6H_{11}		C_6H_6	
	$C_0 = 0.233 \text{ M}$	$C_0 = 0.70 \text{ M}$	$C_0 = 0.233 \text{ M}$	$C_0 = 0.70 \text{ M}$	$C_0 = 0.233 \text{ M}$	$C_0 = 0.70 \text{ M}$
$C_6H_{11}SO_2OCH_3$	—	0.26	0.50	0.40	0.20	0.20
$C_6H_{11}SO_2OC_6H_{11}$	—	—	—	—	—	—
Total acidity	1.02	1.03	0.53	0.61	1.14	1.20
CH_3COCH_3	0.38	0.57	—	—	—	—

TABLE 4. Radiometric Analysis of Products of Reaction of Peroxide with Isopropyl Alcohol (initial activity 1,000,000 pulses/min for 0.0105 mole)

Products isolated	Activity	
	pulses/min	%
Distilled iso- C_3H_7OH	264000	26.40
CH_4	635700	63.57
$C_6H_{11}SO_3Na$	20400	2.04

Among the products of decomposition of peroxide in cyclohexane was cyclohexene. Its formation can be attributed to a disproportionation reaction of cyclohexyl radicals [7]. Hexachloroethane was found in the case of reaction of per-

* The "cage" effect is discussed inter alia by Swain, Schaad and Kresge [7] (Translator).

** The authors have to thank Yu. A. Kaplin for carrying out the radiometric analysis.

TABLE 5.*Experiments on the Thermal Decomposition of the Peroxide

	Iso- C ₆ H ₅ OH	Cyclo- C ₆ H ₁₁	C ₆ H ₆	CCl ₄	Notes
Peroxide sample (millimoles)	10.50	10.45	10.65	10.60	
Duration of experiment (hr)	24	6	7	6	
Temperature of decomposition	20°	35°	50.4°	55.4°	
Products of reaction (millimoles)	10.00	10.05	5.70	9.86	A content of 0.018 g Cl ⁻ in the case of CCl ₄ was found by mercurimetric determination
CH ₄ C ₆ H ₁₁ SO ₃ H	6.36 8.16	6.35 5.53	2.95 6.37	— 6.15	S-Benzylthiuronium derivative m.p. 182-183° (from aqueous alcohol)
C ₆ H ₅ SO ₃ H	0.29	0.87	2.85	3.40	By the bromide-bromate method on the dry salts
C ₆ H ₁₁ SO ₂ OCH ₃	2.64	—	2.07	1.82	Radiometrically in the case of isopropyl alcohol; iodometrically in the case of CCl ₄ [11]
C ₆ H ₁₁ SO ₂ OC ₆ H ₁₁	—	4.15	—	—	M.p. 49.5-50.5° (from cyclohexane) (the literature gives m.p. 51-52°)
CH ₃ COCH ₃	6.00	—	—	—	1.42 g; m.p. of 2,4-dinitrophenylhydrazone 124° (from alcohol) (the literature reports 126°)
CH ₃ COOH	0.20	—	3.58	—	Qualitative determination by cacodyl oxide formation
C ₆ H ₁₀	—	0.7	—	—	By bromination in alcoholic solution
CH ₃ Cl	—	—	—	6.60	
C ₂ Cl ₆	—	—	—	2.40	M.p. 184-185° (in sealed capillary) (the literature gives m.p. 186°)
HCl	—	—	—	0.90	Mercurimetrically [12]
Resin (g)	—	—	0.3	Trace	

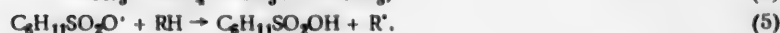
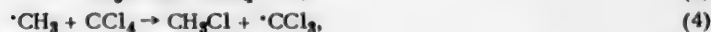
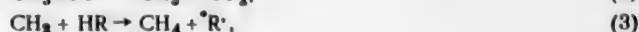
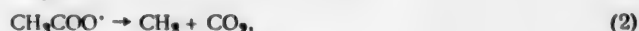
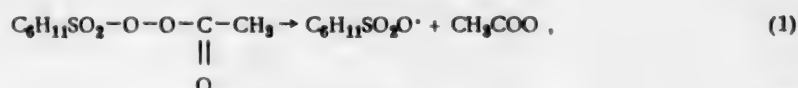
* Volume of solvent in each experiment 15 ml.

oxide with carbon tetrachloride. It is formed by recombination of $\cdot\text{CCl}_3$ radicals. Secondary products were hydrogen chloride and carbonyl chloride, the first of which is evidently the consequence of hydrolysis of $\text{R}'\text{CCl}_3$, while the second is formed by oxidation of the $\cdot\text{CCl}_3$ radical [8].

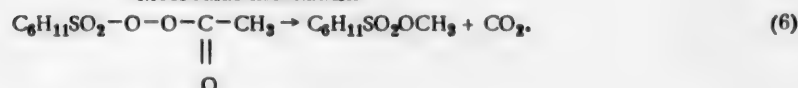
Reaction of acetylcyclohexanesulfonyl peroxide with benzene led to separation of much acetic acid (Table 2), but products of interaction with the solvent were not detected. This result at first sight appears inconsistent, but it can be accounted for by considerable resinification. The nature of the resin could only be elucidated by decomposition of the peroxide in benzene labeled with C^{14} . Radiometric analysis revealed an activity in the resin (400 pulses/min) equal to 2/3 of the initial activity in the benzene (616 pulses/min). The presence of sulfur in the resin was confirmed by qualitative test. The results show that benzene participates in the reaction [9].

The kinetic investigations of thermal decomposition of the peroxide, in conjunction with the analytical results and the nature of the isolated products, enable us to propose two reaction routes—a free-radical mechanism and molecular interaction

Radical-chain mechanism



Molecular mechanism



(RH = hydrogen-containing solvent)

EXPERIMENTAL

Acetylcyclohexanesulfonyl peroxide was synthesized by Graf's method [1]. The content of the substance in the preparation was never lower than 93.5% in any of the experiments. Acetic anhydride labeled with C^{14} in the CH_3 group, needed for preparation of the initial peroxide, was synthesized from acetyl chloride and C^{14} -labeled sodium acetate. The latter was synthesized by a modification of the literature method [10]. Excess of CO_2 was injected into the reaction mixture. The solvents were purified by the usual methods.

Kinetic investigations were carried out in ampoules (in the absence of air). The sealed ampoules were placed in a thermostat at a temperature constant to within $\pm 0.1^\circ$. At predetermined intervals of time the ampoules were withdrawn from the thermostat, quickly cooled, and opened. The contents were then analyzed.

Thermal decomposition of the peroxide was carried out in a reactor to which a reflux condenser was attached through a ground-glass joint. It was fitted with a nitrogen supply tube. The apparatus was placed on a water bath. About 0.0105 mole of peroxide and 15 ml of the solvent were usually charged into the reactor. The system was previously filled with dry nitrogen. The gaseous reaction products were passed through a trap containing 30% KOH solution, where the CO_2 was retained, and the residual gas was collected in a gasholder. At the end of the reaction, a very slow stream of dry nitrogen was passed through the system. The collected gas was analyzed in a VTI apparatus. The acid reaction products were washed with water and titrated with 0.1 N alkali solution. The organic layer was dried over sodium sulfate; the solvent was distilled and the residue analyzed for its content of ester by saponification with alcoholic KOH. The neutralized solution was distilled with steam. Cyclohexanesulfonic acid was identified in the residue through the melting point of its S-benzylthiuronium derivative.

The distillate always contained a small quantity of oily product. The solvent came over initially during decomposition in isopropyl alcohol. Results of the experiments and the conditions of operation are set forth in Table 5.

SUMMARY

1. It was established that thermal decomposition of acetylcyclohexanesulfonyl peroxide with organic solvents takes place according to a first-order kinetic law. The rate depends on the nature of the solvent and falls in the sequence: isopropyl alcohol > cyclohexane > benzene > carbon tetrachloride.

2. It was shown that reaction of acetylcyclohexanesulfonyl peroxide with organic solvents is realized by two routes—a free-radical and a molecular mechanism. This is confirmed by the constancy of the amount of methyl ester in the reaction products which is independent of the change of concentration of the initial peroxide.

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INVESTIGATION IN THE FIELD OF C-ACYLATION OF HETEROCYCLIC KETOENOLS

IV. 5-ACYLBARBITURIC ACIDS

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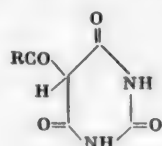
pp. 281-283, January, 1961

Original article submitted December 26, 1959

Among the countless number of 5-monosubstituted barbituric acid derivatives described in the literature, the almost complete lack of study of the 5-acyl derivatives is attracting attention. Only 5-acetyl- and 5-benzoylbarbituric acids have been described, having been prepared reacting barbituric acid with the corresponding acid anhydride [1].

Continuing the work on the study of the C-acylation of heterocyclic ketoenols [2-4], we found that good yields of 5-acylbarbituric acids can be readily obtained by acylating barbituric acid with aliphatic acids in the presence of phosphorus oxychloride. 5-Acylbarbituric acids form colorless, acicular crystals, poorly soluble in water and alcohol, readily soluble in hot acetic acid. They possess sharply defined acidic properties, such as being readily soluble in alkalis; with an alcoholic solution of ferric chloride they give an orange-red coloration.

TABLE 1. 5-Acylbarbituric Acids



R	Yield (%)	Melting point	Molecular formula	Analytical results (%)					
				C		H		N	
				found	calc.	found	calc.	found	calc.
CH ₃	86	295—297°	C ₈ H ₆ O ₄ N ₂	42.30, 42.28	42.35	3.67, 3.79	3.55	16.52, 16.52	16.46
C ₂ H ₅	70	242—244	C ₇ H ₈ O ₄ N ₂	45.76, 45.94	45.65	4.28, 4.38	4.37	15.38, 15.44	15.21
n- C ₃ H ₇	78	224—225	C ₈ H ₁₀ O ₄ N ₂	48.29, 48.27	48.46	5.01, 4.87	5.08	14.33, 14.25	14.13
iso- C ₃ H ₇	25	230—233		48.21, 48.19		4.83, 4.89		14.04, 14.09	
n- C ₄ H ₉	75	218—218.5		50.97, 51.08	50.93	5.80, 5.75	5.70	13.36, 13.17	13.20
iso- C ₄ H ₉	70	213—213.5		50.91, 51.11		5.48, 5.57		13.17, 13.14	
n- C ₅ H ₁₁	77	210—210.5	C ₁₀ H ₁₄ O ₄ N ₂	53.29, 53.39	53.08	6.41, 6.42	6.23	12.39, 12.52	12.38
n- C ₆ H ₁₃	79	205	C ₁₁ H ₁₆ O ₄ N ₂	54.96, 55.02		6.83, 6.72		11.56, 11.63	
n- C ₇ H ₁₅	30	210	C ₁₂ H ₁₈ O ₄ N ₂	57.04, 56.94		7.39, 7.54		11.07, 11.08	

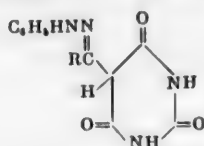
The phenylhydrazones of all the 5-acylbarbituric acids have been synthesized as white, crystalline substances, soluble in alkali, poorly soluble in the majority of organic solvents. The phenylhydrazones crystallize from a

mixture of alcohol and glacial acetic acid as fine needles, melting with decomposition and not giving a color reaction with ferric chloride solution.

EXPERIMENTAL

5-Acetylbarbituric Acid. A mixture of 3 g of barbituric acid, 15 ml of glacial CH_3COOH , and 6 ml of POCl_3 was boiled for 45 minutes under a reflux condenser. On cooling, the reaction mixture was diluted with 150 ml of water, the precipitate obtained filtered off, washed with water, and dried at $\sim 100^\circ\text{C}$. A yield of 3.43 g (86%) of 5-acetylbarbituric acid was obtained. After recrystallizing from dilute CH_3COOH , m.p. was $295-297^\circ$ (with decomp.). A sample of this substance mixed with a sample obtained by the method described in [1] did not give a melting point depression. Other 5-acylbarbituric acids were prepared similarly. Results of experiments are given in Table 1. Phenylhydrazones of 5-acylbarbituric acids were prepared by the usual method in a solution of glacial acetic acid (see Table 2).

TABLE 2. Phenylhydrazones of 5-Acylbarbituric Acids



R	Melting point (with de-comp.)	Molecular formula	Analytical results (%)						
			C		H		N		
			found	calc.	found	calc.	found	calc.	
CH ₃	308—310°	C ₁₃ H ₁₄ O ₃ N ₄	56.93,	56.92	4.89,	5.14	20.69,	20.42	
C ₂ H ₅	241—242		56.90	—	5.12	—	20.64	—	
n-C ₃ H ₇	248—249		58.35,	58.32	5.75,	5.59	19.44,	19.43	
			58.55	—	5.70	—	19.26	—	
iso -C ₃ H ₇	272—275	C ₁₄ H ₁₆ O ₃ N ₄	—	—	—	—	19.41,	—	
n -C ₄ H ₉	228—229		—	—	—	—	19.32	—	
			59.79,	59.58	6.11,	6.00	18.58,	18.53	
iso -C ₄ H ₉	226—226.5		59.75	—	6.25	—	18.46	—	
n -C ₅ H ₁₁	228—228.5		59.50,	—	6.02,	—	18.59,	—	
			59.37	—	5.86	—	18.42	—	
iso -C ₅ H ₁₁	228—228.5	C ₁₆ H ₂₀ O ₃ N ₄	61.07,	60.74	6.53,	6.37	17.56,	17.71	
n -C ₆ H ₁₃	230—230.5		61.11	—	6.66	—	17.52	—	
			61.93	61.80	7.07	6.71	16.86,	16.96	
n -C ₇ H ₁₅	230.5—231		—	—	—	—	16.88	—	
n -C ₇ H ₁₅	230.5—231		62.52	62.77	7.39	7.02	16.39,	16.26	
			—	—	—	—	16.26	—	

SUMMARY

By reacting barbituric acid with aliphatic acids in the presence of phosphorus oxychloride, a series of previously undescribed 5-acylbarbituric acids was prepared.

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THE ORIENTATING INFLUENCE OF SUBSTITUENTS
IN THE FORMATION OF α -SUBSTITUTED PHENAZINE
SALTS. V

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In a previous communication [1] the orientating influences of various substituents occurring in the β -positions in the phenazine ring on formation of phenazine salts were investigated. In the present article these investigations are extended to α -substituents of phenazine where, besides electronic effects transmitted through the phenazine ring, the steric hindrance shown by the following substituents plays a considerable part in the orientation: CH_3 -, OCH_3 -, C_6H_5 - groups, and the chlorine atom. The investigation is based on the spectrophotometric method [2], supported by chemical data. Isomeric monoacid salts of substituted phenazine are compared with corresponding quaternary salts; diacid salts are compared with quaternary salts soluble in concentrated sulfuric acid, in which they are protonated at the free nitrogen in the ring. Spectra of such protonated quaternary salts and spectra diacid salts are often similar as regards the form of the absorption curve and the position of the main maximum, although the latter for the diacid salt is slightly displaced to the short-wave side.

1-Methylphenazine. The methyl group through its induction +I effect exerts negligible influence on the electronic configuration of the phenazine ring; thus, the spectra of phenazine and its methyl homolog are almost identical (Fig. 1, curves 1, 2).^{*} In dilute acid 1-methylphenazine dissolves with formation of a certain amount of monoacid salt, the solution having a dark-yellow color. The absorption band characteristic for a monoacid salt lies at 380-382 m μ (Fig. 2, curves 2-5). In concentrated acid a diacid 1-methylphenazine salt is formed, the solution of which has a bright-orange color. The band of the diacid salt lies at 410-413 m μ (Fig. 2, curve 6).

Onset of protonation in 1-methylphenazine and in unsubstituted phenazine differ; in 2.5% acid phenazine remains as the base [1], while 1-methylphenazine in acid of the same concentration is partially converted into the monoacid salt. This is seen by the recurvature in the absorption curve (Fig. 2, curve 2) at 380 m μ , which in acid of greater concentration is converted into the clearly defined band of the monosalt (curves 4, 5).

The absorption spectra of 1,9- and 1, 10-dimethylphenazinium perchlorates are very similar to each other (Fig. 2, curves 7,9), but the absorption of the monoacid salt of 1-methylphenazine differs so much from them that it is impossible by comparing them to determine at the expense of which of the 2 centers of basicity the monoacid salt is formed. It is most likely that both nitrogen atoms are protonated separately in acid and form two isomeric monoacid salts, the salt with the proton attached to nitrogen atom 10 predominating slightly owing to the absence of steric hindrance in that position. Curve 4 in Fig. 2 represents the absorption spectrum of a solution in which two isomeric monoacid salts and a certain amount of unreacted base are present simultaneously. In 75% acid a small amount of diacid salt is formed, as is shown by the slight recurvature in curve 5 between 400 and 420 m μ (Fig. 2, curve 5). In 96% acid all of the base and almost all of the monoacid salt are converted into the diacid salt, with a band at 413 m μ and ϵ 27,000 (Fig. 2, curve 6).

By reacting dimethyl sulfate with the base at 90-95°, the quaternary salt of 1-methylphenazine is formed smoothly in almost quantitative yield, a sample of which melts without melting point depression when mixed with the 1,10-dimethylphenazinium salt, their spectra also coinciding. A second isomeric quaternary salt is not formed owing to steric hindrance. However, if the 10-position in 1-methylphenazine is occupied by oxygen, for instance, then at a higher temperature and with a large excess of dimethyl sulfate steric hindrance can be overcome and a methyl group introduced into the 9-position. It combines with nitrogen atom 9, forming the methyl sulfate of the

^{*} Explanations to the figures are in the text.

10-oxide of 1,9-dimethylphenazinium in 53% yield. This salt is rather unstable and on repeated crystallization from dilute alcohol is partially decomposed with formation of the 10-oxide of 1-methylphenazine. The diquaternary 1-methylphenazine salt is not formed. Its prototype is the salt formed on dissolving 1,10-dimethylphenazinium perchlorate in concentrated sulfuric acid, its maximum occurring at 419 m μ (Fig. 2, curve 8).

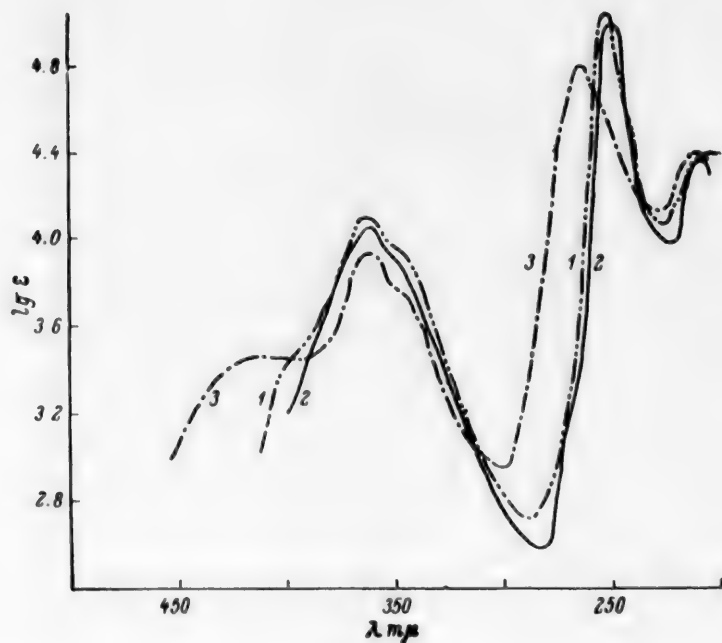


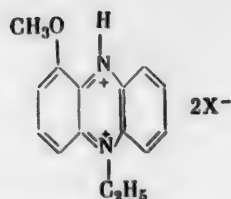
Fig. 1.

The mono- and diacid 1-methylphenazine salts in acid solution are alcoholated on dilution with alcohol, whereupon the absorption band maxima and their molecular extinctions are gradually changed in the reverse order to salt formation.

1-Methoxyphenazine. Introduction of a OCH_3 group into the phenazine ring in the 1-position causes a shift in the absorption spectrum of phenazine at 249 m μ to the extent of 10-20 m μ toward the long-wave region and the appearance of a new band of low intensity at the border of the visible and ultraviolet regions. The phenazine band at 362 m μ remains in the same position in this case (Fig. 1, curve 3). In acid, 1-methoxyphenazine, like all α -substituted derivatives, forms mono- and diacid salts with characteristic absorption bands. For monoacid salts the band maximum lies at 381-382 m μ ; for the disalt it occurs between 405 and 412 m μ . In 7.5% acid, judging by the presence of two maxima in the absorption curve, some of the 1-methoxyphenazine molecules remain as the free base (Fig. 3, curve 2), and some are converted into the monosalt (maximum at 381 m μ).

In view of the complete coincidence the absorption spectra of the two isomeric quaternary salts, 1-methoxy-10-methylphenazinium (Fig. 3, curve 7) and 1-methoxy-9-methylphenazinium (Fig. 3, curve 9*) perchlorates, it is impossible to decide at the expense of which of the two nitrogen atoms the monoacid salt is formed. Evidently, as in the preceding case, because of steric hindrance in dilute acid the protons combine at first with nitrogen atom 10. In 7.5% acid protonation of the second nitrogen atom begins, this atom being shielded by the CH_3O group; the disalt is then formed, as is evident by the curve's low-intensity recurvature at 410 m μ (Fig. 3, curve 4), this being small and less than in unsubstituted phenazine [1], where the shielding factor is absent. In 90% acid the disalt of approximately half the molecules is formed (Fig. 3, curve 5). The remaining molecules are monosalt. There is no base in this solution. In 96% acid neither base nor monoacid salt is in solution; they are completely protonated at both centers of basicity. Thus, the absorption curve of the diacid salt with a maximum at 412 m μ (Fig. 3, curve 6) is very similar in form and position to the curve of the 1-methoxy-10-ethylphenazinium salt in 96% acid (Fig. 3, curve 8).

* Curve 9 (Fig. 3) coincides with curve 7.



1-Chlorophenazine. A chlorine atom in the 1-position in the phenazine ring withdraws electrons from both nitrogen atoms, because of its $-I$ effect, to a greater extent from nitrogen atom 9, which is nearer. Because of this, the strength of the basicity and the ability of 1-chlorophenazine to form salts in comparison with phenazine decreases. It is known that chlorophenazines react with dimethyl sulfate with much greater difficulty than unsubstituted phenazine, a higher temperature and a large excess of dimethyl sulfate being needed. As a result of this, in the absorption curve of 1-chlorophenazine in dilute sulfuric acid (from 2.5 to 7.5%) the form and position of the absorption bands is unchanged, a salt not being formed in such acid. However, already in 9% acid, as can be judged by the appearance of a band with a maximum at $380\text{ m}\mu$, some of the molecules of the base in solution are converted into monoacid salt (Fig. 4, curve 2).

Further increase in acid concentration leads to accumulation of the monoacid salt in solution, (Fig. 4, curves 3, 4). We could not determine its structure by comparison with the two isomeric quaternary salts of 1-chlorophenazine because of the absence of 1-chloro-9-methyl-phenazinium perchlorate. Synthesis of this salt from the 10-oxide of 1-chlorophenazine, in spite of numerous attempts, was not achieved because, of the two isomeric 9- and 10-oxides of 1-chlorophenazine, the second is practically unreactive to dimethyl sulfate. The reason for this is evidently the volume of the substituent and the attraction to it of electrons from nitrogen atom 9.

To attach a proton to a monoacid salt molecule at the second nitrogen atom, a large excess of acid is necessary; 90% acid concentration is insufficient. Only in 96% acid is the monosalt converted into disalt, the band maximum of which lies at $412\text{ m}\mu$ (Fig. 4, curve 5). Such a band is evident for 1-chloro-10-ethylphenazinium perchlorate in concentrated sulfuric acid (Fig. 4, curve 7), but it is slightly displaced toward the long-wave side. In the case of isomeric 2-chlorophenazine disalt forma-

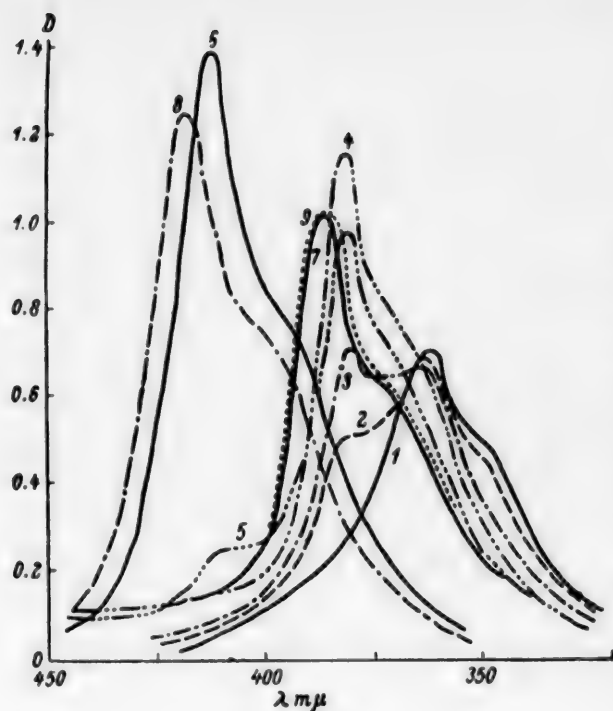


Fig. 2.

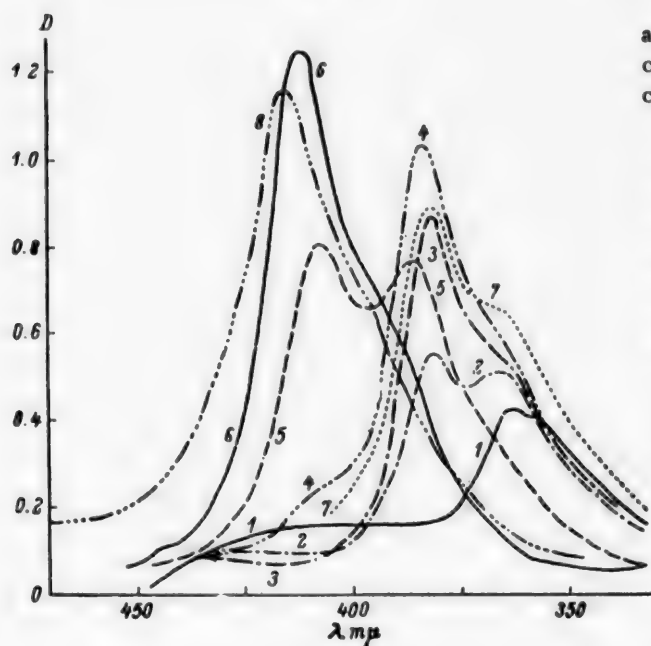


Fig. 3.

tion begins under milder conditions, even on reaction with 45% acid [1]. This difference can be explained by the influence of steric hindrance in 1-chlorophenazine and its absence in 2-chlorophenazine where only electronic influences are evident in substituent orientation.

On reacting 1-chlorophenazine with dimethyl sulfate we obtained only one isomer, 1-chloro-10-methylphenazinium methyl sulfate, which was identified by the compound obtained by reducing the methyl sulfate of 1-chloro-10-methylphenazinium 9-oxide with zinc dust in water.

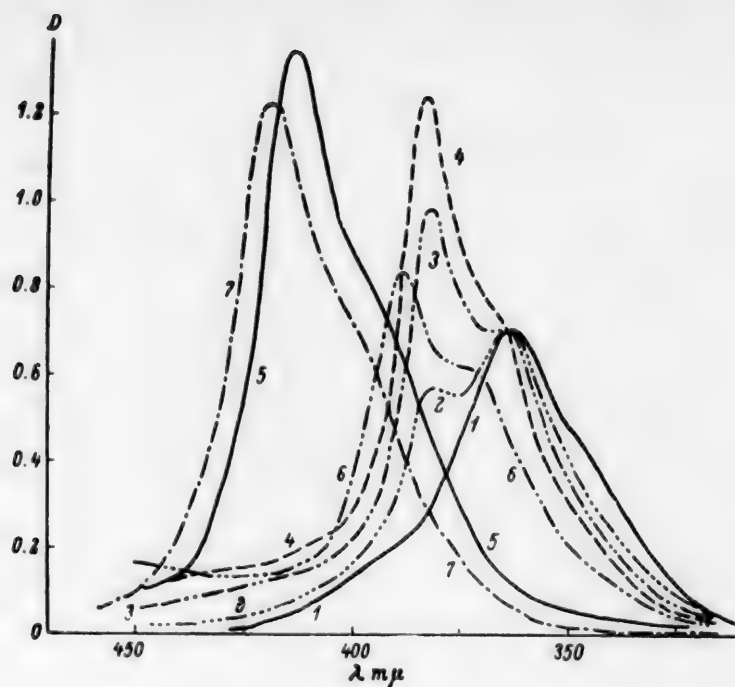


Fig. 4.

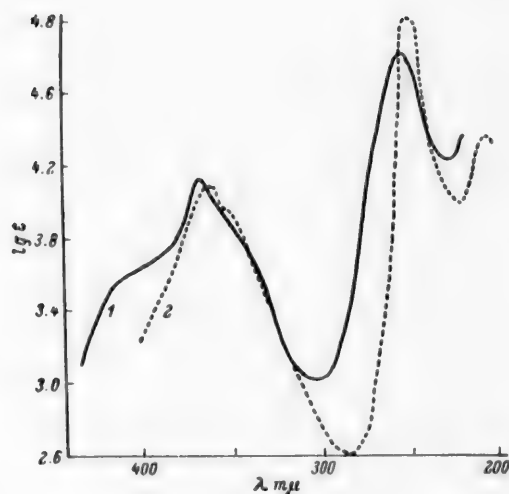


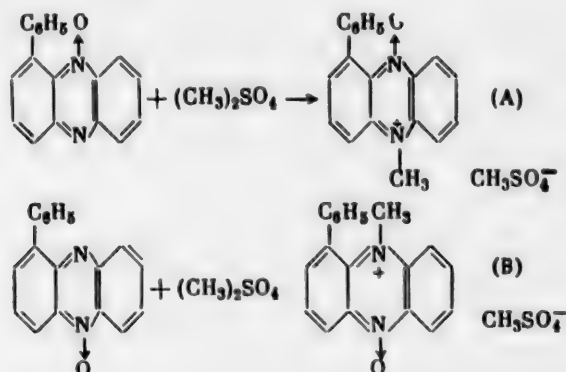
Fig. 5.

1-Phenylphenazine. In a previous communication [1] it was shown that a C_6H_5 group in the 2-position in the phenazine ring attracts electrons from nitrogen atom 9 with which it is coupled, as a result of which the whole spectrum of the phenazine is displaced to the long-wave side. A phenyl group in the 1-position in a similar manner, although to a slightly less extent, affects nitrogen atom 10. This effect is made apparent in the absorption bands towards the long-wave side (Fig. 5, curve 1); they lie at $252 m\mu$, ϵ 63,000 and $356 m\mu$, ϵ 13,100. Besides this, a new absorption band is evident as a recurvature on the border of the visible region at $400 m\mu$, ϵ 4400 (Fig. 5, curve 1).

1-Phenylphenazine in acid is converted into the mono- and diacid salts. In acid it dissolves readily, giving the orange coloration pertaining to the monoacid salt ion (Fig. 6, curve 2), the band maximum of which lies at $383 m\mu$. With increase in acid concentration monosalt content in solution increases; at the same time, the monosalt band intensifies and the band of the base weakens (Fig. 6, curves 3,5).

The question as regards to which of the two nitrogen atoms in the phenazine ring protons are joined, forming a monoacid salt, is decided by comparing the monosalt curve with the two curves of the isomeric quaternary salts of 1-phenylphenazine. In Fig. 6 (curves 3,5,6) the monoacid salt band is similar to the absorption band of 1-phenyl-10-methylphenazinium perchlorate and differs from the absorption band of the second isomeric salt. Accordingly, the monoacid salt is formed by protonation of nitrogen atom 10. Attachment of protons to nitrogen atom 9 in dilute sulfuric acid is hindered by the presence of the bulky phenyl group in the 1-position. Its shielding effect is surmounted by protons in high concentration of the latter. In 96% acid protons combine not only with nitrogen atom 10, but also with nitrogen atom 9. A diacid salt is formed, the solution of which has a dark-orange color. The absorption maximum of the diacid salt lies at $415 m\mu$, ϵ 18,000 (Fig. 6, curve 4). A similar band, only slightly displaced to the long-wave side, occurs for the quaternary salt of 1-phenylphenazine dissolved in concentrated sulfuric acid (Fig. 6, curve 7).

Steric hindrance on the part of the C_6H_5 group in 1-phenylphenazine and its influence on the withdrawal of electrons from nitrogen atom 10 are evident in the conversion reactions of the 9- and 10-oxides of 1-phenylphenazine into the isomeric quaternary salts (A) and (B).



At reaction temperature $120-125^\circ$, salt (A) is formed in 43% yield. Steric hindrance of the substituent plays no part here; attraction of electrons from nitrogen atom 10 to the substituent and the associated weakening of the basicity of the ring do not allow an increase in the yield indicated. Salt (B) is not formed at the same temperature. If the temperature is held at $135-140^\circ$ for 20 minutes, salt (B) is formed in 72% yield. Absence of combination of the phenyl group with nitrogen atom 9 favors combination of the methyl group with it, but the steric proximity of the substituent prevents this. At higher temperature this hindrance is overcome, and a satisfactory yield of salt (B) is obtained.

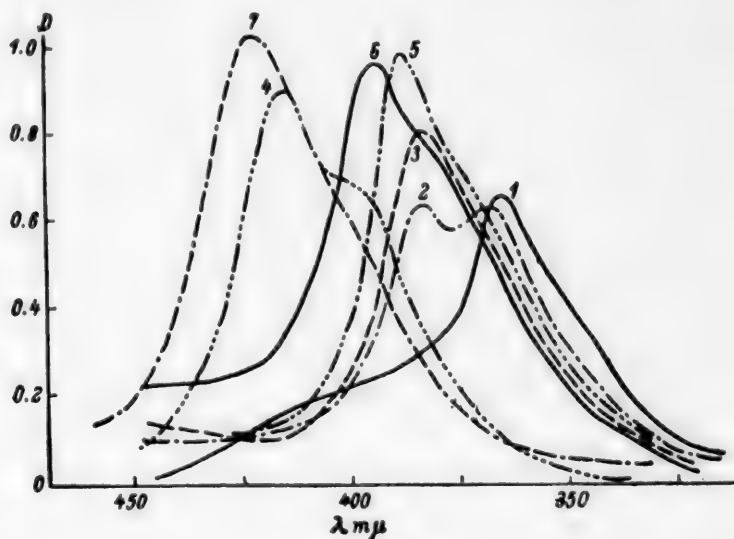


Fig. 6.

The electron-accepting properties of the phenyl group as a substituent in the phenazine ring cause differing resistance of the isomeric quaternary salts of 1-phenylphenazine to alcoholysis. The salt with a methyl at nitrogen 9, in spite of the strain caused by the steric proximity of the substituent, is quite stable and does not undergo alcoholysis in 5 days. The isomeric salt with a methyl at nitrogen atom 10, in which steric hindrance is absent but attraction of electrons to the phenyl group takes place, is nearly 28% alcoholated in the first 6 hours and after 10 hours, 38%. In Fig. 7 is shown a series of absorption curves portraying the gradual conversion over a period of time of 1-phenyl-10-methylphenazinium perchlorate into 1-phenylphenazine in alcoholic solution. To determine the degree of alcoholysis, two simultaneously prepared solutions of identical concentration ($3 \cdot 10^{-5}$ m/liter) of the isomeric quaternary 1-phenylphenazine salts were examined by spectrophotometry over predetermined intervals of time in that band of wavelengths where the most marked changes in the spectrum during alcoholysis were observed; temperature during

the time indicated remained constant (19.5°). As standards for comparison, on the spectral curves we chose two points at one place on the wavelength axis and two points at another, using a freshly prepared solution of 1-phenyl-10-methylphenazinium perchlorate (curve 1) and a solution of 1-phenylphenazine (curve 6). Optical densities were read at 253 and 267 m μ . Over the period of time indicated, the curve of 1-phenyl-9-methylphenazinium perchlorate remained unchanged, but the curve of 1-phenyl-10-methylphenazinium perchlorate approached the curve of 1-phenylphenazine in form and wavelength position.

Alcoholysis of 1-Phenyl-10-methylphenazinium Perchlorate

Time (hours)	Readings of optical densities (D) from absorption curves						% found in solution		$K = \frac{\Delta \lg C}{\Delta T} \cdot 2.303$
	A_x	A_{xx}	A_{yx}	A_y	A_{yy}	A_{xy}	of base	of quaternary salt	
	readings at 253 m μ			readings at 267 m μ					
0	—	1.110	0.820	—	1.030	0.60	—	100	—
2	0.850	1.110	0.820	1.02	1.030	0.60	5.9	94.1	0.0304
4	0.900	1.110	0.820	0.99	1.030	0.60	17.1	82.9	0.0468
6	0.960	1.110	0.820	0.97	1.030	0.60	27.8	72.1	0.0546
10	1.090	1.110	0.820	0.83	1.030	0.60	37.7	62.3	0.0474

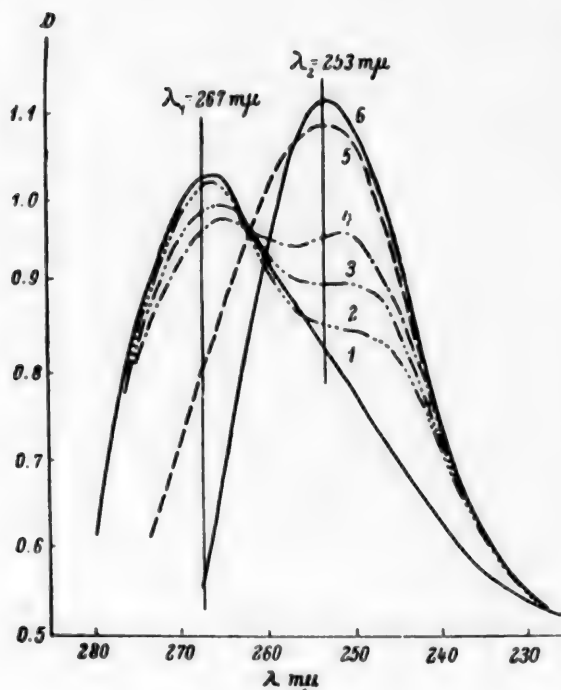


Fig. 7.

Data on the measurements and calculation of the quantitative proportions in solution of the salt and base and values for the hydrolysis constant are shown in the table.

EXPERIMENTAL

1-Methylphenazine, pale-yellow needles with m.p. 108° (108° [3]). 1-Chlorophenazine, pale-yellow needles with m.p. 122-123° (122-123° [4]). 1-Methoxyphenazine, yellow needles with m.p. 169° (169° [5]). 1-Phenylphenazine, yellow needles with m.p. 157° (157° [6]).

1,9-Dimethylphenazinium perchlorate was prepared by reducing the methyl sulfate of the 10-oxide of 1,9-dimethylphenazinium with zinc dust in water [7]. Dark-yellow plates with m.p. 199°, temp. of decomp. 203° (from 50% alcohol).

Found %: N 9.02, 8.99. $C_{14}H_{13}O_4N_2Cl$. Calculated %: N 9.07.

1,10-Dimethylphenazinium perchlorate was prepared similarly to the above from the methyl sulfate of the 9-oxide of 1,10-dimethylphenazinium. Yellow needles with m.p. 203-204°. A sample mixed with 1,9-dimethylphenazinium perchlorate melted at 192° (decomp.).

Found %: N 9.07, 8.87; Cl 11.58, 11.57. $C_{14}H_{13}O_4N_2Cl$. Calculated %: N 9.07; Cl 11.51.

1-Chloro-10-ethylphenazinium perchlorate, golden plates with m.p. 248°. The sample was submitted by V. P. Chernetskii. Recrystallized twice from 50% alcohol.

Found %: N 8.02, 8.21; Cl 20.92, 20.88. $C_{14}H_{12}O_4N_2Cl_2$. Calculated %: N 8.16; Cl 20.70.

1-Phenyl-9-methylphenazinium perchlorate, brown needles with m.p. 180°, temp. of decomp. 195-196° (m.p. 180, temp. of decomp. 195-196° [6]). 1-Phenyl-10-methylphenazinium perchlorate, brownish-yellow needles with

m.p. 214°, temp. of decomp. 217° (m.p. 214°, temp. of decomp. 217° [6]).

1-Methoxy-10-ethylphenazinium perchlorate. 2.24 g of 10-ethylphenazone-1 was dissolved in 100 ml of dry benzene, 5 ml of neutral dimethyl sulfate added, and boiled on an oil bath for 1 hour. The color of the solution gradually changed to dark red. The precipitate of quaternary salt after cooling was filtered and washed with benzene and ether. Yield was 3.33 g (95%). The salt was dissolved in 15 ml of alcohol and precipitated as the perchlorate. The sample after crystallization from 50% alcohol formed small shining yellow needles with m.p. 256° (decomp.).

Found %: N 8.02, 8.14. $C_{15}H_{15}O_5N_2Cl$. Calculated %: N 8.27.

1-Methoxy-9-ethylphenazinium perchlorate, brown plates with a metallic luster. The sample was prepared from the ethyl sulfate of the 10-oxide of 1-methoxy-9-ethylphenazinium by reduction with zinc dust in water with a yield of 60%. M.p. 248° (decomp.). A sample mixed with 1-methoxy-10-ethylphenazinium perchlorate had m.p. 237° (decomp. 237-240°).

Found %: N 8.15, 8.31. $C_{15}H_{15}O_5N_2Cl$. Calculated %: N 8.27.

SUMMARY

Using the spectrophotometric method of analysis, the processes in the formation of the mono- and diacid salts of 1-methyl-, 1-chloro-, 1-methoxy-, and 1-phenylphenazines were studied; absorption spectra were determined for the quaternary and acid salts of the bases indicated. The alcoholysis constant was calculated for the rather unstable salt 1-phenyl-10-methylphenazinium perchlorate. It was shown that in the case of α -substituents of phenazine, protonation (and alkyl addition) proceeds via the nitrogen atom free of the shielding effect of the substituent.

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ORIENTATION IN SUBSTITUTION IN THE AROMATIC SERIES

VII. CATALYSTS IN THE ISOMERIZATION OF DICHLOROBENZENES

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We have previously [1,7] described experiments on the isomerization of the dichlorobenzenes at temperatures from 100 to 180°C in the presence of aluminum chloride. Recently a series of patents have appeared in which various conditions for carrying out the process in the presence of aluminum chloride are proposed [2,4-6]. In addition to those mentioned, attention is also drawn to the work in which is described isomerization at temperatures above 172°, i.e., at increased pressure [3].

In the present communication, experiments using other compounds as catalysts are described, experiments using mixtures of them with aluminum chloride, and experiments studying the catalytic activity of various samples of aluminum chloride.

EXPERIMENTAL

Catalysts for isomerization of p-dichlorobenzene were investigated. The latter, together with the simple and complex catalysts investigated, was heated in a sealed ampoule in a thermostat at 160° for 15 hours. The reaction mixture was then treated with water, the product separated, dried, distilled in vacuo, and analyzed for para-isomer content by the thermal method [8].

The first series of experiments, carried out with 0.1 mole of catalyst to 1 mole of dichlorobenzene, showed that Al_2O_3 , B_2O_3 , MgSO_4 , BiCl_3 , ZnCl_2 , NiCl_2 , HgCl_2 , SnCl_2 , PbCl_2 , and polyphosphoric acid do not catalyze the process, p-dichlorobenzene remaining unchanged after the experiment. Under the same conditions with AlCl_3 , 17.5% of the p-dichlorobenzene reacts, and with $\text{AlCl}_3 \cdot \text{HSO}_4$, 4%.

In Table 1 are shown the results of experiments using mixtures of 0.1 mole of aluminum chloride with other compounds also used in the proportion of 0.1 mole to 1 mole of p-dichlorobenzene.

The results of this series of experiments in adding various oxides showed that V_2O_5 , WO_3 , and P_2O_5 lower the rate of isomerization. Oxides of Mo, B, Hg, Be, Ca, Cu, Fe, and Al, although they can act as catalysts in the presence of AlCl_3 , show a weaker action than the same additional amount of AlCl_3 ; and, finally, oxides of Cr, Zn, Ti, and Mg mixed with AlCl_3 act more effectively than AlCl_3 .

The results obtained in a series of experiments in adding metallic chlorides showed that the chlorides of Sn, Na, Pb, Bi, and Cu lower the activity of AlCl_3 ; the chlorides of Ni, Ca, and Zn, and also polyphosphoric and sulfuric (0.04 mole) acids increase the reaction rate somewhat, but to a lesser degree than introduction of a further 0.1 mole of aluminum chloride; and finally, that mercuric chloride and 0.01 mole of sulfuric acid significantly increase AlCl_3 activity.

In the experiments described, magnesium oxide and 0.01 mole of sulfuric acid as the additive showed the greatest activity. This induced us to investigate magnesium sulfate as an additive, this being catalyst of even greater activity (the last experiment, Table 1).

In the second series of experiments the action of various mixtures of aluminum chloride and magnesium sulfate was studied. For 1 mole of p-dichlorobenzene, 0.1 mole of AlCl_3 and various amounts of MgSO_4 were used. The mixtures were heated for 5 hours at 160°.

TABLE 1. The Action of Two-Component Catalysts on the Isomerization of p-Dichlorobenzene

Catalyst	% $\text{C}_6\text{H}_4\text{Cl}_2$ isomerized	Catalyst	% $\text{C}_6\text{H}_4\text{Cl}_2$ isomerized
$\text{AlCl}_3 + \text{V}_2\text{O}_5$	3.3	$\text{AlCl}_3 + \text{SnCl}_2$	0.6
$\text{AlCl}_3 + \text{WO}_3$	6.1	$\text{AlCl}_3 + \text{NaCl}$	4.8
$\text{AlCl}_3 + \text{P}_2\text{O}_5$	11.7	$\text{AlCl}_3 + \text{PbCl}_2$	7.2
AlCl_3 (0.1 mole)	17.5	$\text{AlCl}_3 + \text{BiCl}_3$	12.8
$\text{AlCl}_3 + \text{MoO}_3$	20.7	$\text{AlCl}_3 + \text{CuCl}$	13.7
$\text{AlCl}_3 + \text{B}_2\text{O}_3$	22.8	AlCl_3 (0.1 mole)	17.5
$\text{AlCl}_3 + \text{HgO}$	23.2	$\text{AlCl}_3 + \text{NiCl}_2$	22.4
$\text{AlCl}_3 + \text{BeO}$	24.4	$\text{AlCl}_3 + \text{CaCl}_2$	22.9
$\text{AlCl}_3 + \text{CaO}$	24.9	$\text{AlCl}_3 + \text{ZnCl}_2$	25.4
$\text{AlCl}_3 + \text{CuO}$	37.9	$\text{AlCl}_3 + \text{H}_2\text{SO}_4$	28.8
$\text{AlCl}_3 + \text{Fe}_2\text{O}_3$	40.7	(0.04 mole)	
$\text{AlCl}_3 + \text{Al}_2\text{O}_3$	41.0	$\text{AlCl}_3 + \text{PPA}$ *	36.5
AlCl_3 (0.2 mole)	43.6	AlCl_3 (0.2 mole)	43.6
$\text{AlCl}_3 + \text{Cr}_2\text{O}_3$	49.8	$\text{AlCl}_3 + \text{HgCl}_2$	52.0
$\text{AlCl}_3 + \text{ZnO}$	51.4	$\text{AlCl}_3 + \text{H}_2\text{SO}_4$	59.0
$\text{AlCl}_3 + \text{TiO}_2$	59.3	(0.01 mole)	
$\text{AlCl}_3 + \text{MgO}$	60.2	$\text{AlCl}_3 + \text{MgSO}_4$	67.9

* PPA - polyphosphoric acid.

TABLE 2. Results of Sublimation and Isomerization of p-Dichlorobenzene with 0.1 mole of AlCl_3 at 160° for 15 hours

AlCl_3 sample	% AlCl_3 sublimed	% p-Dichlorobenzene isomerized
GOST 4452-48	98.7	5
VTU 3500-52	98.6	10
After prolonged storage	96.7	28
"	95.5	30
"	87.0	33

TABLE 3. Isomerization of p-Dichlorobenzene with 0.1 mole of AlCl_3 , type GOST 4452-48

Time ampoule with AlCl_3 remained open	Change in weight of AlCl_3 (in g)	% p-Dichlorobenzene isomerized
0	—	4.3
30 minutes	+0.0008	7.3
2 hours	+0.0005	8.4
24 hours	+0.0008	29.4
72 hours	-0.0003	41.2

experiments given in Table 3 show that after storage in air aluminum chloride activity increases.

In the literature [9] many instances are described where addition of water activates aluminum chloride. In the experiments carried out by us on isomerization with addition of water to the reaction mixture, increase in reaction

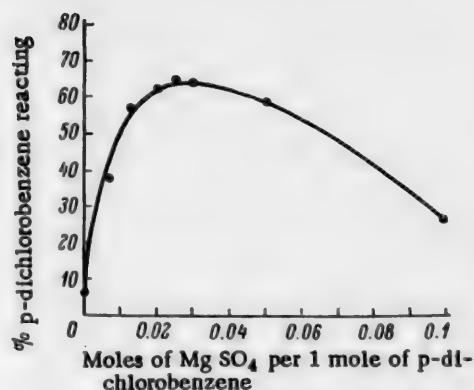


Fig. 1. Effect of amount of MgSO_4 on isomerization of p-dichlorobenzene.

The results of the experiments, presented in Fig. 1, show that the most effective action is obtained by using a mixture containing 0.025-0.03 mole of MgSO_4 and 0.1 mole of AlCl_3 . In another series of experiments the amount of MgSO_4 was kept constant and equal to 0.025 mole, but the amount of aluminum

chloride was increased from 0.01 to 0.2 mole. The experiments showed that reaction rate increases steadily with increase in amount of AlCl_3 .

It was also noticed that the catalytic activity of aluminum chloride depends on its degree of purity, period and conditions of storage. It is known that only absolutely pure AlCl_3 sublimes without leaving a residue [9]. We selected a weighed amount of AlCl_3 and sublimed it. AlCl_3 content of the sample under investigation was estimated from the residue remaining after sublimation. This method gave reproducible results. Thus, in five determination of the one sample, values of from 98.5 to 99% were obtained for the sublimed product.

We investigated the catalytic activity and degree of purity by sublimation of a number of samples of aluminum chloride of different types and storage time. The results of the experiments, given in Table 2, show that the purer the aluminum chloride (according to the results of sublimation), the less its activity. A specimen of the first sample (GOST 4452-48) was sublimed by us into a reaction tube, and the reaction carried out on the sublimate. 5.4% of the p-dichlorobenzene isomerized, i.e., AlCl_3 activity remained low.

We conjectured that AlCl_3 activity changes according to the change in its constitution on storage. To investigate this the following experiments were carried out. A weighed sample (about 0.4 g) of AlCl_3 was placed in an ampoule and left open. After exposure to the atmosphere, p-dichlorobenzene was introduced; the ampoule was sealed and heated at 160° for 15 hours. Results of the

TABLE 4. Isomerization of p-Dichlorobenzene in the Presence of 0.1 mole of AlCl_3 , to which has been Added Water and from which Hydrogen Chloride has been Removed

Moles of H_2O used per 1 mole of AlCl_3	HCl required to be removed (in g)	HCl actually removed (in g)	HCl given off after heating (in g)	% p-Dichlorobenzene isomerized
0	—	—	—	2.5
0.048	0.0028	0.0024	0.0025	12.0
0.186	0.0182	0.0182	0.0132	27.6
0.241	0.0280	0.0298	0.0129	25.5
0.470	0.0395	0.0397	0.0404	25.5
0.620	0.0669	0.0674	0.0323	28.0
0.90	0.0837	0.0717 *	0.0403	0
1.32	0.1573	0.1168 *	0.0507	0

* Evolution of hydrogen chloride lasted for 2.5 months.

TABLE 5. Isomerization of Dichlorobenzene at 200° in the Presence of AlCl_3 , Al_2O_3 , and MgSO_4

Heating time (hours)	Isomer	Constitution of mixture after isomerization (in %)		
		ortho-	para-	meta-
0.5	ortho-	70.7	7.6	21.7
	para-	4.6	91.8	3.6
	meta-	11.8	8.0	80.2
1	ortho-	60.7	10.3	29.0
	para-	4.2	80.3	15.5
	meta-	12.2	12.0	75.8
2	ortho-	45.4	17.4	37.2
	para-	4.5	66.8	28.7
	meta-		21.4	
4	ortho-	33.8	22.6	43.6
	para-	11.1	43.6	45.3
	meta-	12.2	29.3	58.5
8	ortho-	19.7	27.4	52.9
	para-	12.3	33.1	54.6
	meta-	11.8	30.7	57.5
10	ortho-	20.3	27.1	52.2
	para-	12.3	31.5	56.2
	meta-	16.8	30.1	53.1

Thus, the experiments show that increase in aluminum chloride activity resulting from addition of water or the use of AlCl_3 that has been in contact with the atmosphere is explained by the formation of aluminum oxide in the mixture. To determine the optimum ratio of AlCl_3 to Al_2O_3 , a series of experiments was carried out in which total AlCl_3 and Al_2O_3 amounted to 0.1 mole per 1 mole of p-dichlorobenzene and, besides that, 0.025 mole of magnesium sulfate. The results of the experiments, given in Fig. 2, show that 1/4 of the AlCl_3 can be successfully by aluminum oxide.

From all the above information it follows that isomerization of dichlorobenzene can be carried out with a considerably less amount of aluminum chloride than was used previously [1,7], and at a greater rate. This is achieved by partial replacement of aluminum chloride by its oxide, by addition of magnesium sulfate, and by elevating isomerization temperature. The latter proved possible because on using a mixture of $\text{AlCl}_3 + \text{MgSO}_4$ no residual pressure arises in the ampoule after carrying out the reaction and subsequent cooling. Resinification products in this case also are almost completely absent.

Thus, a series of experiments is presented dealing with the isomerization of dichlorobenzene at 200° with a catalyst consisting of $\text{AlCl}_3 : \text{Al}_2\text{O}_3 : \text{MgSO}_4 = 0.05 : 0.0125 : 0.0125$ mole per mole of dichlorobenzene. The results of the experiments, given in Table 5, show that under these conditions a state close to equilibrium can be reached in less than 8 hours.

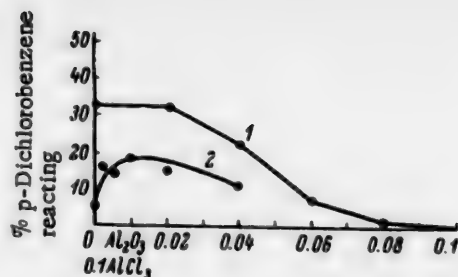


Fig. 2. Influence of a series of factors on the isomerization of p-dichlorobenzene (0.1-0 mole of AlCl_3 , 0-0.1 mole of Al_2O_3 per mole of p-dichlorobenzene; temperature 160°). 1) 0.025 mole of MgSO_4 per mole of p-dichlorobenzene, time 2 hours; 2) without MgSO_4 , time 15 hours.

rate was also observed, but we were unable to establish any regular relationship between rate and the amount of water introduced, evidently because water accelerates the reaction and the hydrogen chloride evolved retards it [7]. To remove the latter, the ampoule of aluminum chloride and water was stoppered, left open in a vacuum desiccator for 24 hours, and stored for a considerable time over solid caustic potash at 50-55°. After removal of hydrogen chloride, p-dichlorobenzene was added according to the loss in weight (allowing for 1 mole of HCl per 1 mole of water), and the ampoule heated at 160° for 5 hours. The results of the experiments, presented in Table 4, show that after removal of hydrogen chloride, catalyst activity increases with increase in water added, is then maintained at a certain level, and finally falls to zero. A further experiment, carried out with addition of dry aluminum hydroxide to the AlCl_3 , showed that catalyst activity does not increase as a result of this addition.

SUMMARY

1. 27 different metallic oxides, their chlorides, and other substances were tried as catalysts in the isomerization of dichlorobenzenes. It was found that as an additive to the aluminum chloride magnesium sulfate possesses the greatest activity.

2. The activity of various samples of aluminum chloride was studied. It was found that the pure reagent possesses little activity. Addition of water, leading to the formation of aluminum oxide, markedly increases aluminum chloride activity.

3. An effective catalyst, consisting of AlCl_3 , Al_2O_3 , and MgSO_4 , is suggested.

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THE CHEMISTRY OF POLYMYXIN M

I. QUALITATIVE AMINO ACID COMPOSITION, END GROUP ANALYSIS

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In the literature are described several related polypeptide antibiotics, all belonging to the polymyxin group. To them belong in the first instance, strictly, polymyxins A, B₁, B₂, C, D, E [1]. Polymyxins are effective against a whole series of gram-negative bacteria, and what is particularly important, they depress the growth of the blue-superpurative bacillus *Pseudomonas pyocyanea*, which is stable toward the majority of other antibiotics. Polymyxins B and E have found practical use. To the polymyxin group are closely related also circulins A and B [2-4], polypeptins A and B [5], cholistins A, B, and C [6-7], and cholimylin [8-9]. Chemical investigation of the antibiotics of this group has shown that they all have certain characteristic features in common: 1) all are polypeptides; 2) all contain diamino-butyric acid, threonine, and an aliphatic acid; 3) all possess a basic character and do not contain free carboxyl or α -amino groups.

The most closely investigated have been polymyxins B [10-13] and circulin A [14], for which the sequence of the amino acids in the molecule has been established and a cyclopeptide structure demonstrated. Polymyxins A, C, and E have received less study.

In 1946, a strain of the polymyxin-forming *Bacillus polymyxa* Ross. was isolated from Moscow soils by V. S. Rossovskii [15]. A method for isolation and purification of this antibiotic using ionites was developed by A. S. Khokhlov, S. M. Mamiofe, and Z. T. Sinitsina [16]. Preparatory study of the chemical and biological properties of this native polymyxin carried out at the All-Union Scientific Research Antibiotic Institute and in the Protein and Antibiotics Chemistry Laboratory of the Faculty of Chemistry at Moscow State University showed that it is a new polymyxin variant, to which was given the name polymyxin M [17].

Amino acid constitution and certain properties of polymyxin antibiotics so far described are given in Table 1.

In this work the results are given of electrophoretical investigations of polymyxin M, determinations of its amino acid constitution, and end group analysis.

Polymyxin M investigation by paper electrophoresis was carried out in buffer solutions over the pH interval 2.0 to 9.8. In every case, polymyxin M gave one spot moving to the cathode. Rate of movement decreases noticeably with increase in pH of the buffer, but even at pH 9.8 is not equal to zero. From this data it follows that polymyxin M is an electrophoretically homogeneous substance, possessing clearly defined basic properties. The electrophoretical behavior of polymyxin B was studied in parallel. It was shown that both antibiotics are very similar in electrical properties (Table 2).

The qualitative amino acid constitution of polymyxin M was studied using distributive paper chromatography in five solvent systems. The following amino acids were used as standards: arginine, lysine, ornithine, α , γ -diamino-butyric acid, glycine, alanine, serine, threonine, homoserine, leucine, norleucine, isoleucine, phenylalanine, proline, asparaginic and glutaminic acids. As a result, it was established that α , γ -diaminobutyric acid, threonine, and leucine enter into the constitution of polymyxin M (Table 3).

These data were confirmed by two-dimensional chromatography of the polymyxin hydrolyzate carried out in turn in the systems methanol-water-pyridine (40:10:2) and butanol-1-methyl ethyl ketone-water-diethylamine (20:20:10:2), and by preparative isolation of amino acids from the polymyxin hydrolyzate. Separation of diamino-

TABLE 1. Amino Acid Constitution of Known Polymyxin Antibiotics

Name of antibiotic	Source	Molecular wt.	Amino acids							Aliphatic acid
			α, γ -diaminobutyric acid	threonine	leucine	isoleucine	serine D	phenylalanine D	valine D	
Polymyxin A	<i>Bacillus</i>	1293	⊕	⊕	⊕	⊖	⊖	⊖	⊖	6-Methyloctanoic
Polymyxin B ₁	<i>Aerosporus</i>	1220	5L + 1D	2L	1	⊖	⊖	1	⊖	Isopelargonic
Polymyxin B ₂	<i>B. Polymyza</i>		5L + 1D	2L	1	⊖	⊖	1	⊖	C ₈ -Acid
Polymyxin C		1150	⊕	⊕	⊖	⊖	⊖	⊕	⊖	⊕
Polymyxin D			5L	3L	1D	⊖	1	⊖	⊖	6-Methyloctanoic
Polymyxin E			⊕	⊕	D	⊖	⊖	⊖	⊖	The same
Circulin A and B	<i>B. circulans</i>	1500	6L	2L	1D	1L	⊖	⊖	⊖	• •
Cholistin A, B and C	<i>B. collistinus</i>	—	5L	1L	1D + 1L	⊖	⊖	⊖	⊖	• •
Polypeptin A and B	<i>B. krzeminski</i>	—	3D	1L	2L	1	⊖	1	1	⊕
Cholimycin	<i>B. collistinus</i>	—	4	1	1	⊖	⊖	⊖	⊖	⊕

Note:

1. The figures in the columns indicate the number of corresponding amino acid residues in the antibiotics shown.

2. The signs ⊕ and ⊖ indicate the presence or absence of the given amino acid or unknown aliphatic acid residue in the case of antibiotics whose quantitative constitution has not been established.

TABLE 2. Electrophoresis of Polymyxin M

pH	Current strength (beginning-end) (ma per cm of zone width)	Duration of expt. (hr)	Distance to spot (cm) of polymyxin		Mobility of polymyxin · 10 ⁻⁴ (cm ² v ⁻¹ sec ⁻¹)	
			M	B	M	B
2.00	0.1—0.1	2.00	6.5	7.5	1.13	1.3
3.00	0.18—0.24	2.75	8.5	8.5	1.30	1.30
4.50	0.17—0.20	3.00	7.6	7.3	0.88	0.84
7.00	0.31—0.58	3.00	5.7	5.5	0.6	0.64
8.60	0.08—0.08	3.00	2.1	2.1	0.24	0.24
9.85	0.12—0.18	3.00	0.3	0.3	0.034	0.034

butyric acid from neutral amino acids was carried out on sulfopolystyrene cationite KU-2 in H⁺ form. The neutral amino acids were washed from the cationite with 5% pyridine, and 2.5% ammonia used for eluting the diaminobutyric acid. Threonine and leucine were then separated by distributive chromatography on a column of powdered paper. The amino acids isolated were characterized by paper chromatography in several systems and by analysis of elements.

An aliphatic acid was isolated from the ethereal extract of the polymyxin M hydrolyzate. From paper chromatography in the system butanol-1—ammonia (1.5 N) this acid occupies a position corresponding to an aliphatic acid with 8-10 carbon atoms. In its properties and from analysis of elements the p-bromobenzylthiouronic salt obtained by us from the acid under investigation corresponds to the salt of 6-methyloctanoic acid. These data indicate that in the composition of polymyxin M enters an aliphatic acid near to, or possibly identical to, 6-methyloctanoic acid.

TABLE 3. Chromatography of Hydrolyzate of Polymyxin M

Name of amino acid "standard"	R _{th} value					
	n-butanol - water acetic acid (4 : 5 : 1)		phenol - nitrate, 4-phosphate buffer		n-butanol - water acetic acid (49,5 : 49,5 : 1)	
	standards	hydroly- zate	standards	hydroly- zate	standards	hydroly- zate
α , γ -Diaminobutyric acid	0.47	0.47	0.16	0.16	0.27	0.27
Ornithine	1.07		0.18			
Glutamic acid	1.00		0.26			
Threonine	1.00	1.00	1.00	1.00	1.00	1.00
Homoserine	0.90		2.30			
Norleucine	2.40					
Isoleucine	2.22	2.20	7.40			
Leucine	2.30		7.40	7.40	7.80	7.80
Phenylalanine	2.20		7.40			

Note. Lysine, arginine, serine, glycine, alanine, proline, and asparaginic acid were also used as "standards", but are not included in the table because in the solvent systems shown their R_{th} values differed considerably from R_{th} for the amino acids of the polymyxin M hydrolyzate.

To determine the free amino groups, by whose presence is explained polymyxin's basic properties, we used the method of Sanger [18]. On treating polymyxin M with excess 1-fluoro-1, 4-dinitrobenzene in aqueous acetone solution in the presence of triethylamine, dinitrophenylpolymyxin M was obtained. According to the data of paper electrophoresis, DNP*-polymyxin M did not contain any trace of polymyxin. DNP-polymyxin was subjected to hydrolysis by heating with a mixture of glacial acetic, 85% formic, and concentrated hydrochloric acids (1:1:2) in a sealed ampoule for 14 hours at 105°. By paper chromatography it was established that the DNP-polymyxin M hydrolyzate contains γ -DNP-diaminobutyric acid and free amino acids: diaminobutyric acid, threonine, and leucine. No α -DNP-amino acids were found in the hydrolyzate. Thus, the γ -amino groups of α , γ -diaminobutyric acid are the free groups of polymyxin M. There are no free α -amino groups in its molecule.

The presence in the DNP-polymyxin M hydrolyzate of an unsubstituted diaminobutyric acid deserves special attention. By a special experiment it was shown that it could not be formed in the course of DNP-polymyxin hydrolysis at the expense of γ -DNP-diaminobutyric acid decomposition. It was thus established that at least one molecule of α , γ -diaminobutyric acid participates in formation of amide linkages not only of the α - but also of the γ -amino group, and as a result of this is not subjected to dinitrophenylation. It is possible that in polymyxin M, branching of the peptide chain occurs with participation of one of the amine groups of α , γ -diaminobutyric acid, similar to that occurring in polymyxin B.

The electrophoretic behavior of polymyxin M and its DNP derivative indicate the presence in it of free carboxyl groups. To confirm this an attempt was made to detect C-terminal amino acids in the polymyxin, using the method of Akabori [19]. The polymyxin was subjected to rupture by heating with anhydrous hydrazine. After removal of excess hydrazine and extraction of amino acid hydrazides with enathol, the aqueous layer was investigated chromatographically. In this instance no free amino acids were detected in it, this pointing to the absence in polymyxin M of carboxyl groups.

The results of end-group determination indicate that polymyxin M, similarly to other antibiotics of this group, has a cyclopeptide structure.

Thus, the antibiotic investigated by us in its constitution and basic chemical properties is a typical representative of the antibiotic-polymyxin group.

EXPERIMENTAL

Polymyxin M. The study of its chemical properties was carried out on a sample of the sulfate of polymyxin M S-717 (VNIIA) with activity 10,000 units/mg, this being a slightly yellowish powder, readily soluble in water, less

*Here and henceforth the abbreviation DNP is used for dinitrophenyl.

so in methanol and other alcohols, insoluble in hydrocarbons, ketones, and esters. M.p. 224-228° (decomp.), $[\alpha]_D^{25} -48.1^\circ$ (c 2.505, H₂O). Polymyxin M gives positive ninhydrin and Biuret reactions (λ_{\max} 555 mμ). The ratio of α-amino nitrogen (determined by the Van Slyke method in an Ioanisiu apparatus [20]) to total nitrogen (by the Kjeldahl method) was equal to 0.48.*

Electrophoresis. Polymyxins B and M were subjected to paper electrophoresis in the apparatus described by Durham [22]. As electrolytes, buffer solutions of the following composition were used: a) pH 2 : 5% acetic acid; b) pH 3.0 : 37.5 ml 2 M HCOOH, 20.0 ml 1M NH₄OH, 942.5 ml water; c) pH 4.5 : 14.7 ml 2M CH₃COOH, 20.0 ml 1 M NH₄OH, 965.3 ml water; d) pH 7.0 : 26 ml 2M CH₃COOH, 50 ml 1 M NH₄OH, 924 ml water; e) pH 8.6 : 50 ml 0.1 M NaHCO₃, 9 ml 0.1 N NaOH, 531 ml water; f) pH 9.85 : 0.01 M Na₂CO₃.

Onto a strip of paper impregnated with the corresponding buffer were introduced solutions of polymyxins B and M (10 mg in 1 ml) in amounts of 5 μl at each point. On completion of the experiment, the strips were dried and developed with ninhydrin. The mobility of the antibiotics (without allowance for osmosis) was calculated from the formula:

$$u = \frac{d \cdot l}{t \cdot E},$$

where: u is mobility, in cm²·v⁻¹·sec⁻¹; d is distance covered by substance on passage to cathode, in centimeters; l is length of paper strips between surfaces of electrolyte in electrode vessels, in centimeters (in every case $l = 27.5$ cm); t is duration of experiment, in seconds; E is voltage, in volts (a storage battery of voltage 220 v was used).

Results of mobility determinations are given in Table 2.

Hydrolysis of Polymyxin M. A solution of 50 mg of polymyxin M sulfate in 5 ml of 6 N hydrochloric acid was heated in a sealed ampoule for 24 hours at 105-108°. Hydrochloric acid was removed by repeated distillation in vacuo with water; the residue was dissolved in 1 ml of 85% formic acid and this solution used for chromatography.

Chromatography of Hydrolyzate. To identify the amino acids of the hydrolyzate one-dimensional chromatography (descending method) was used chiefly. In some cases to improve separation the solvent was allowed to drain from the lower edge of the sheet. On to a sheet of chromatographic paper (Type "V" of Volodarskii Leningrad factory) was applied 5 μl of hydrolyzate and amino acid "standard" solutions (10 mg in 1 ml). Chromatography was carried out in the following solvent systems: 1) butanol-1-water-acetic acid (4;5;1); 2) butanol-1-water-acetic acid (49.5; 49.5;1); 3) phenol saturated with citrate-phosphate buffer (6.3 % sodium citrate + 3.7% KH₂PO₄); 4) tert-butyl alcohol-methyl ethyl ketone-85% formic acid-water (160;160;1;30); 5) butanol-1-acetic acid-water (144;13;43).

To develop the dried chromatograms they were placed in 0.5% ninhydrin solution in acetone, and were then held at room temperature until the color developed fully. The results obtained are given in Table 3. The possibility of the presence of leucine and isoleucine in the polymyxin M hydrolyzate was checked in systems 4 and 5, and R_{th}^{**} for leucine was 3.66 and 4.0, and for the corresponding hydrolyzate spot 3.66 and 4.1. The value of R_{th} for isoleucine in these solvent systems equalled 3.40 and 3.30 respectively. Identification of phenylalanine was carried out by the method of Pasleka and Morgan [23].

Preparative Isolation of Amino Acids from Polymyxin M Hydrolyzate. Hydrolysis of Polymyxin M. 5 g of polymyxin M hydrochloride ("impure raw material"***) was dissolved in 50 ml of 6N hydrochloric acid and heated in a sealed ampoule for 24 hours at 106-108°. After removal of aliphatic acid by ether extraction, the hydrolyzate was concentrated in vacuo. Excess hydrochloric acid was removed by distillation with several amounts of water. The dark oily residue was dissolved in water and boiled with 0.5 g of animal charcoal. The charcoal was filtered off and washed several times with hot water. The filtrate and wash water were united and concentrated in vacuo. A light-yellow oil was formed.

*It should be noted that this value is anomalously large; however, a similar high value for α-amino nitrogen, determined by the Van Slyke method, was also observed for other antibiotics of this group (polymyxin D [21] and circulin [3]).

** $R_{th} = L_x/L_{th} = R_f x/R_{f th}$, where L_x is the distance covered by the unknown amino acid; L_{th} is the distance covered by threonine.

***In view of the lack of pure antibiotic, for isolation of amino acids a sample of polymyxin raw material was used, containing a considerable amount of impurities.

Isolation of α , γ -Diaminobutyric Acid from Neutral Amino Acids. The amino acid mixture obtained was dissolved in 50 ml of distilled water and the solution passed through two columns (60 x 2.5 cm) cationite KU-2 in H⁺ form, 25 ml into each, at the rate of 15 ml per hour. The solution flowing out showed a negative ninhydrin reaction. The columns were washed with distilled water and then through them was passed a 5% aqueous pyridine solution. 20- to 25-ml fractions were collected. The fractions showing a positive ninhydrin reaction were analyzed chromatographically in system 1. They contained threonine, leucine, and traces of a substance with R_{th} 0.75, 1.23, and 2.0,* but contained no α , γ -diaminobutyric acid. The eluates were united and concentrated in vacuo. 1.138 g of amino acid mixture was obtained.

Isolation of α , γ -Diaminobutyric Acid. On completion of elution of neutral amino acids (negative ninhydrin reaction) the column was washed with 2.5% aqueous ammonia. The fractions containing α , γ -diaminobutyric acid were united and concentrated in vacuo. The oil obtained was adjusted with dilute hydrochloric acid to pH 2 and α , γ -diaminobutyric acid dihydrochloride precipitated from solution by a volume of anhydrous alcohol 5 times as great as the solution. The precipitate was dissolved in water and boiled with animal charcoal. The α , γ -diaminobutyric acid dihydrochloride isolated from solution was twice recrystallized from an aqueous solution of anhydrous alcohol. 0.66 g of chromatographically pure α , γ -diaminobutyric acid was obtained.

Found %: C 24.44, 24.38; H 5.90, 6.05; N 14.78, 14.79. $\text{C}_4\text{H}_{12}\text{O}_2\text{N}_2\text{Cl}_2$. Calculated %: C 24.44; H 6.28; N 14.71.

Separation of Threonine and Leucine Mixture. The amino acids were separated on a column (2.5 x 65 cm) filled with powdered paper prepared in the following manner. 10 sheets of chromatographic paper (52 x 65 cm) were wetted with distilled water, torn to pieces, drenched with 5 liters of 5% nitric acid, and boiled for 10 minutes. The mass of paper obtained was washed with distilled water until universal indicator gave a neutral reaction, dried in a drying oven at 110-120°, ground in a ball mill and sifted through a 0.25 mm mesh sieve. The homogeneous powder obtained was drenched with the upper layer of the system butanol-1-water-acetic acid (4:5:1) and the suspension formed transferred to the column. The solvent was passed through the column under low pressure for 24 hours, then a solution of 1.132 g of amino acid mixture carefully poured onto the wet surface of the mass of paper, and the solvent passed through the column at the rate of 15 ml/hour. Fractions of 4-5 ml were collected. The fractions were analyzed chromatographically in system 1. Fractions containing only one amino acid (threonine or leucine respectively) were united and concentrated in vacuo. The mixed fractions were discarded. 0.222 g of unpurified leucine and 0.558 g of threonine were obtained. The amino acids isolated were purified by boiling their solutions with animal charcoal and by reprecipitating twice from the water by alcohol. 0.205 g of chromatographically pure threonine and 0.170 g of leucine were obtained.

Found %: C 40.42, 40.31; H 7.91, 7.76; N 11.50, 11.36. $\text{C}_6\text{H}_{13}\text{O}_3\text{N}$. Calculated %: C 40.30; H 7.56; N 11.70.

Found %: C 54.48, 54.62; H 10.04, 10.16; N 11.14, 11.24. $\text{C}_6\text{H}_{15}\text{O}_2\text{N}$. Calculated %: C 54.9; H 10.2; N 10.6.

Isolation of Aliphatic Acid. An ethereal extract of the hydrolyzate of 5 g of polymyxin M was frozen in a mixture of dry ice and acetone to remove water, and the ether was then distilled off. We obtained 223.4 mg of a dark-brown oil.

Preparation of p-Bromobenzylthiuronate of the Aliphatic Acid. To 170 mg of unpurified aliphatic acid was added a 1N caustic potash solution until a bright-red color was obtained with phenolphthalein, and then 0.5 g of p-bromobenzyl bromide dissolved in hot alcohol. The precipitate settling out was filtered off and dried in vacuo over sulfuric acid. 257 mg of unpurified p-bromobenzylthiuronate was obtained. The p-bromobenzylthiuronate obtained was recrystallized twice from 96% alcohol. M.p. 158°. The following melting points were noted for the p-bromobenzylthiuronates of the aliphatic acids isolated from polymyxins A, B, and D: 159, 160, 158-158.5° respectively.

Found %: C 50.38, 50.27; H 6.97, 6.79; N 6.93, 7.02. $\text{C}_{17}\text{H}_{28}\text{O}_2\text{N}_2\text{SBr}$. Calculated %: C 50.60; H 6.70; N 7.00.

Chromatography of the Aliphatic Acid. Chromatography was carried out according to the method proposed by Reid [24]. Chromatographic paper was kept in an atmosphere of ammonia for 4-5 hours. Then, onto points 3 cm away from each other were placed solutions of the ammonium salts of the acid under investigation and of caprylic and pelargonic acids. As the mobile phase, butanol-1 saturated with 1.5 N ammonia was chosen. The chromatograms were air-dried and developed in one of two ways. a) The chromatogram was sprayed with a 0.04% bromocresol purple solution, diluted with 5 volumes of formalin, and kept for several minutes in an atmosphere of 3% ammonia. The acids appeared as yellow spots on a violet background. b) The chromatogram was placed for 3-5 minutes in a 1% lead

* Pure samples of preparations of polymyxin M did not contain these substances, hence we did not attempt their identification.

acetate solution, carefully washed with distilled water and again air-dried. The dried chromatogram was treated with hydrogen sulfide [25]. The acids appeared as dark-brown spots on a white background. Values for R_f found were: for pelargonic acid 0.74, for caprylic 0.67, for the aliphatic acid isolated from the polymyxin M hydrolyzate 0.74.

Preparation of DNP-Polymyxin M. To a solution of 0.1 g of polymyxin M in 0.6 ml of water were added 0.6 ml of acetone and 0.1 ml of triethylamine, and then 0.23 g of 1-fluoro-2,4-dinitrobenzene added dropwise. The mixture was stirred for 1 hour at room temperature and held at 40° in a thermostat for a further hour. The orange precipitate of DNP-polymyxin separating out was filtered off, washed with ether, and air-dried. Completeness of dinitrophenylation was controlled by paper electrophoresis in 30% acetic acid and in a 0.1 M sodium carbonate solution (pH 9.8). In both cases DNP-polymyxin gave only one yellow spot, situated at the introduction point. After development with ninhydrin no other spots were observed. 0.1018 g of DNP-polymyxin was obtained. M.p. 214-218° (decomp.).

Found %: C 43.42, 43.70; H 6.06, 5.68; N 16.21, 16.16.

DNP-polymyxin is a yellow powder insoluble in water, alcohols, ether, and the majority of organic solvents, poorly soluble in acetone, more readily so in acetic and formic acids.

Hydrolysis of DNP-Polymyxin. To 33.3 mg of DNP-polymyxin were added 2 ml each of glacial acetic and 85% formic acids, and 4 ml of concentrated hydrochloric acid. The mixture was heated in a sealed ampoule for 4 hours at 106°. The hydrolyzate was concentrated in vacuo; excess hydrochloric acid was removed by distillation with several amounts of water. The dry residue was dissolved in 5 ml of water and extracted with ether and ethyl acetate. The ethereal and ethyl acetate fractions were concentrated and analyzed by paper chromatography in the system tert-amyl alcohol-bipthalate buffer (pH 6).

In the ethereal fraction no dinitrophenylamino acids were observed; the ethyl acetate fraction contained γ -DNP-diaminobutyric acid. To the aqueous layer was added an equal volume of concentrated hydrochloric acid and hydrolysis continued for a further 10 hours. The residue obtained after concentrating the hydrolyzate in vacuo was dissolved in 10 ml of water and extracted with butanol-1. The aqueous and butanol layers were analyzed by paper chromatography. Chromatography of the butanol layer was carried out in the system tert-amyl alcohol-bipthalate buffer (pH 6). Only one yellow spot was observed, coinciding with γ -DNP-diaminobutyric acid, used as a standard. The aqueous layer was chromatographed in system 1. After chromatogram development with ninhydrin solution, α , γ -diaminobutyric acid, threonine, and leucine were observed.

Control Hydrolysis of γ -DNP-diaminobutyric Acid. 14.3 mg of γ -DNP-diaminobutyric acid was dissolved in a mixture consisting of 1 ml of glacial acetic acid, 1 ml of 85% formic acid, and 1 ml of water. To the resulting solution was added 3 ml of concentrated hydrochloric acid and the mixture heated in a sealed ampoule for 14 hours at 106°. The residue obtained after distilling off water and hydrochloric acid in vacuo was dissolved in formic acid and investigated chromatographically in the system butanol-1-water-acetic acid (4:5:1). After developing with ninhydrin, on the chromatogram only one spot was observed, corresponding to γ -DNP-diaminobutyric acid.

Detection of Possible Carboxyl Groups in Polymyxin M [26]. 12.3 mg of polymyxin M was dissolved in 1 ml of anhydrous hydrazine and the solution heated in a sealed ampoule at 100° for 6 hours. The solution was concentrated and the dry residue dissolved in 2 ml of water. The solution was extracted twice with 0.5-ml amounts of enanthol. The aqueous layer was concentrated to minimum volume and analyzed by paper chromatography in the system n-butanol-water-acetic acid (4:5:1). On the chromatogram no spots were observed corresponding to the position of the amino acids entering into the constitution of polymyxin M, or of any other amino acids.

SUMMARY

1. The behavior of polymyxin M on paper electrophoresis was investigated, and it was shown that polymyxin M possesses the properties of a strong base and is electrophoretically a homogeneous substance.

2. The qualitative constitution of polymyxin M was studied. It was established that it consists of residues of α , γ -diaminobutyric acid, threonine, leucine, and an aliphatic acid. It was shown that polymyxin M differs in its amino acid constitution from polymyxins B, C, and D, described previously.

3. It was established that the basic nature of this antibiotic is caused by the presence in the molecule of free amino groups, these being the γ -groups of α , γ -diaminobutyric acid. It was shown that one of these α , γ -diaminobutyric acid residues has no free functional groups and participates in the formation of peptide linkages not only of the α - but also of the γ -amine group.

4. It was established that in the polymyxin M molecule there are no free α -amine or carboxyl groups. This is evidence that polymyxin M has a cyclopeptide structure.

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SYNTHESIS OF A PEUCEDANIN AMINO DERIVATIVE

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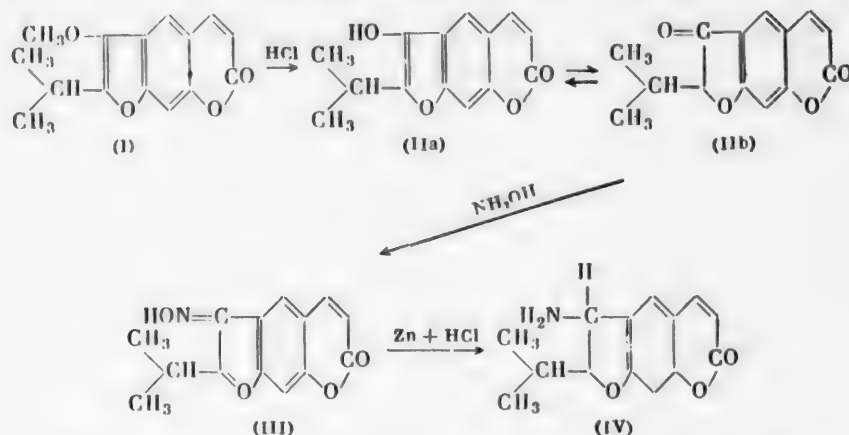
pp. 305-308, January, 1961

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Study of the relationship between the structure and biological activity of a series of natural compounds—coumarins and furocoumarins—has brought about a series of interesting conclusions regarding the influence of various substituents (hydroxy, alkoxy, and alkyl groups) and of double bonds on the activity of these compounds [1-5]. If the anticancerous properties of furocoumarins are being considered, it is of interest to prepare derivatives of these compounds with electropositive substituents in the furan ring and, in particular, amino derivatives whose salts would be water-soluble.

The present communication is devoted to the synthesis of an amino derivative of a natural furocoumarin, peucedanin (4'-methoxy-5'-isopropylfuro-2',3',6,7-coumarin), which possesses antitumorous activity [6]. Peucedanin is obtained from the roots of the Russian brimstonewort (*Peucedanum ruthenicum* L.), family Umbelliferae.

We achieved the synthesis of the amino derivative by saponification of peucedanin (I) into oreozelone (II b), oximation of the latter and reduction of the oxime (III) with zinc dust to the amine (IV).



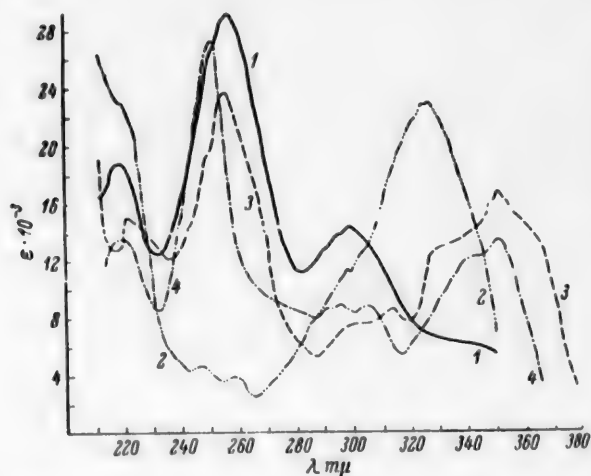
Saponification of peucedanin was carried out with hydrochloric acid in alcoholic solution by the method described in [7] and proceeded with theoretical yield of oreozelone. Preparation of the ketone at this stage was explained by peucedanin's being a methyl ether of the enol form of oreozelone (IIa) [7], the formation of which is conjectured during the biochemical processes of the plant. Single-stage attempts at synthesis of peucedanin by methylation of oreozelone with methyl iodide, dimethyl sulfate, and diazomethane have been unsuccessful until recently and have led to the formation of an isomer. Only lately has this synthesis been successfully achieved, by heating oreozelone with a solution of aluminum chloride in anhydrous methanol [8].

We carried out oximation of oreozelone (II b) in a neutral medium, using excess hydroxylamine hydrochloride. The reaction was accompanied by development of a green coloration in the solution. Reduction of the oxime was carried out with zinc dust in a mixture of acetic and hydrochloric acids. Use of catalytic hydrogenation or reduction with sodium amalgam was excluded in this case because of the possibility of hydrogenating the double bond in the lactone ring.

The resulting amine in alcoholic solution exhibited intense blue fluorescence, disappearing on acidification. An aqueous solution of the nitrate prepared from the amine gave characteristic reactions with alkaloid reagents; on rendering it alkaline with ammonia, a base precipitated, readily soluble in acids. The base was also soluble in caustic alkaline solutions, giving an intense yellow color explained by opening of the lactone ring. On acidification of such a solution the original base could not be obtained.

To characterize the products we examined their ultraviolet absorption spectra.

EXPERIMENTAL



Ultraviolet absorption spectra. 1) Peucedanin; 2) oreozelone; 3) oreozelone oxime; 4) 4'-amino-5'-isopropylfuro-2', 3', 6,7-coumarin.

Oreozelone. To a saturated solution of peucedanin in alcohol was added a tenfold excess of concentrated hydrochloric acid and the mixture heated on a water bath for 20-30 minutes. The viscous, white product was diluted with water (1:2), the liquid drawn off, and the residue washed with water and alcohol. M.p. 177° (from alcohol). Colorless, acicular crystals, readily soluble in chloroform, ether, and caustic alkaline solutions; insoluble in water.

Found %: C 69.05, 69.20; H 4.80, 5.01. $C_{14}H_{12}O_4$. Calculated %: C 68.85; H 4.95.

λ_{\max} 220, 251, 296, 306, 351 mμ.

Oreozelone Oxime. 1.0 g of oreozelone and 1.2 g of hydroxylamine hydrochloride in 2 ml of water were boiled with 20 ml of alcohol for 1.5 hours. During boiling, 10% caustic soda solution was added in small amounts to the liquid so that the mixture remained weakly acidic to litmus. On completion of oximation the liquid was diluted with water (1:2) and the oxime extracted with ether. After removal of ether, the yellow-green residue was recrystallized from alcohol. Colorless crystals with m.p.

200-202° (decomp.), readily soluble in the usual organic solvents and insoluble in water. Yield 0.8208 g (77.4%).

Found %: C 64.90, 65.06; H 5.20, 5.09; N 5.52, 5.59. $C_{14}H_{13}O_4N$. Calculated %: C 64.86; H 5.01; N 5.40.

λ_{\max} 222, 256, 314, 350 mμ.

Reduction of Oreozelone Oxime. 22.7 g of oxime was dissolved in 60 ml of glacial acetic acid, 100 ml of water added, 10 ml of 30% hydrochloric acid, 30 g of zinc dust, and the mixture heated for 4 hours on a water bath in a flask fitted with reflux condenser and stirrer. The liquid was filtered, made alkaline with 25% ammonia solution and the amino derivative extracted with chloroform. From the united chloroform extracts the amino derivative was extracted initially with 10% and then with 5% sulfuric acid solution. The acidic solutions were made alkaline with soda and the amino derivative again extracted with chloroform. After solvent distillation, 7.13 g (34%) of a greenish-yellow resin was obtained, readily soluble in acetone, chloroform, less so in alcohol, ether, and acids, and insoluble in water.

Nitrate of the Amino Derivative. To a cooled solution of the substance in ethyl acetate, concentrated nitric acid was added dropwise until an acidic reaction to litmus was shown. The precipitate appearing after 24 hours was filtered off, washed with ethyl acetate, and recrystallized from methanol. About 5 g of yellowish, acicular crystals was obtained with m.p. 202.5°, readily soluble in water, less so in methanol, and insoluble in organic solvents.

Found %: C 54.95, 54.82; H 5.32, 5.40; N 9.32, 9.20. $C_{14}H_{15}O_3N \cdot HNO_3$. Calculated %: C 54.54; H 5.19; N 9.09.

λ_{\max} 247, 258, 298, 327 mμ.

4'-Amino-5'-isopropylfuro-2', 3', 6,7-coumarin. An aqueous solution of the nitrate of the amine was made alkaline with 10% ammonia solution and the base obtained extracted with chloroform. After solvent distillation and repeated recrystallization from ether and benzene, yellowish, acicular crystals were obtained with m.p. 151°, soluble in alcohol, ether, and chloroform, less so in benzene, and insoluble in water.

Found %: C 68.91, 69.10; H 6.24, 6.33; N 5.37, 5.82. $C_{14}H_{15}O_3N$. Calculated %: C 68.57; H 6.12; N 5.71.

SUMMARY

Synthesis was achieved of N-containing derivatives of a natural furocoumarin peucedanin, and of oreozelone oxime and its corresponding amine.

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ESTABLISHMENT OF THE STRUCTURE OF SOPHORADINE AND LEONTINE

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From the middle Asian plant *Sophora alopecuroides* L., A. P. Orekhov and co-workers isolated a series of alkaloids, the main one of which (quantitatively) was sophoradine [1]. The molecular formula $C_{15}H_{26}ON_2$ was attributed to it.

In spite of attempts to split the molecule of sophoradine by the procedures of Hoffman and of Brown, and also by the aid of the Grignard reaction, no positive result of any kind was obtained; the structure of sophoradine remained moot until recently [2].

Initiating the investigation of sophoradine, we at first tried to establish in it the presence of double bonds, the existence of which in sophoradine one could assume as a consequence of its extreme susceptibility to oxidation (it instantly decolorizes acid permanganate solution). The unsaturated character of sophoradine is also indicated by a positive reaction with tetranitromethane. However, all attempts to obtain by oxidation of sophoradine any kind of characteristic product of breakdown failed.* The presence in sophoradine of a double bond could not be confirmed even by catalytic hydrogenation (according to Adams, and with Raney nickel).

By reduction of sophoradine with lithium aluminum hydride there was obtained a deoxygenated crystalline base of composition $C_{15}H_{26}N_2$.

The inactive character of the atom of oxygen, as well as the absence of basic properties in one of the nitrogen atoms of sophoradine, allows one to assume in it the presence of a lactam group; this is completely confirmed both by the infrared absorption spectra (characteristic band at 1630 cm^{-1}) and by its susceptibility to hydrolysis.

Sophoradine, in contrast to matrine, is with difficulty saponified by caustic potash. But by boiling it with hydrobromic acid there is obtained a hydrobromide salt of an amino acid of composition $C_{15}H_{24}N(=NH)(-COOH) \cdot 2HBr$. Depending on the conditions of hydrolysis, there is obtained in addition to the primary product a small amount of a by-product—too small an amount to investigate in greater detail.

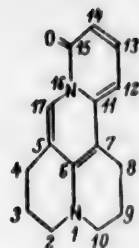
The amino acid obtained from sophoradine possesses a very great tendency to reclose the lactam ring, and attempts to isolate it in free form were not successful. Also, even attempts to esterify sophoradinic acid and its hydrobromide salt led to closure of the lactam ring and to isolation of the original sophoradine.

On the basis of the composition of the derivative of sophoradine described above, its molecular formula should be taken to be $C_{15}H_{24}ON_2$ instead of the earlier accepted $C_{15}H_{26}ON_2$, from which it follows that sophoradine is an isomer of matrine.

Considering that the alkaloids accompanying sophoradine are sophocarpine and sophoramine, which contain the matrine skeleton [3], it was to be expected that sophoradine should also belong to the group of alkaloids with the ring system of matrine, and that it is probably a spatial isomer differentiated by the configuration of one or several asymmetric carbon atoms.

Therefore, it was of great interest to carry out the dehydrogenation of sophoradine under the conditions described by Kondo and Tsuda for matrine [4]. In the molecule of matrine this reaction forms double bonds in positions $C_{17}-C_5$, C_6-C_7 , $C_{11}-C_{12}$, $C_{13}-C_1$, and an optically inactive octadehydromatrine is obtained; the lactam group of matrine remains unchanged.

* Susceptibility to oxidation by potassium permanganate is also observed in the case of matrine, although to a somewhat smaller degree.



We failed to isolate the octadehydro product of sophoradine by dehydrogenation under the conditions stated by the Japanese chemists for matrine. These conditions appeared to be too harsh for sophoradine. The very small yield (the product of the reaction was detected only by paper chromatography) forced us to change the conditions of the reaction. After conducting a series of experiments, we established that lowering the temperature of the reaction to 280–300°, shortening the period of reaction to 30 minutes, and admitting nitrogen creates milder conditions; thanks to this we succeeded in isolating an optically inactive product of dehydrogenation with composition $C_{15}H_{16}ON_2$. The properties of this octadehydrosophoradine and also its ultraviolet and infrared absorption spectra* point to its identity with octadehydromatrine. This is also confirmed by the absence of a depression of the melting point of a mixture of a sample of octadehydromatrine obtained by us and the octadehydrosophoradine.**

Starting from these data, one should reach the conclusion that basically sophoradine has the matrine nucleus, and that it is a spatial isomer of matrine and consequently contains the lactam group in the same position.

At present, the literature contains knowledge of another spatial isomer of matrine which was obtained by Ochiai, Okuda and Minato during hydrogenation of matrine in glacial acetic acid with a platinum catalyst [5]. Along with the product of reduction, the Japanese chemists obtained a base of composition $C_{15}H_{24}ON_2$, named allomatrine, which is a spatial isomer of matrine.

On examination of the properties of allomatrine, our attention was drawn to the similarity of this base to the alkaloid leontine, as is clear from the table.

Alkaloid	[α] _D of base	Melting point		
		base	pic- rate	hydro- chloride
Allomatrine	{ +78.1° (+77)	105–106° (103–105)*	177° (177)	—
Leontine	{ –78.0 (–78.2)	106–108 (107–108)	177 (177)	—
Racemate, obtained by mixture of allo- matrine with leon- tine	{ ±0	86–87	—	219–220°

* In the parentheses are cited the constants found in the literature [5,6].

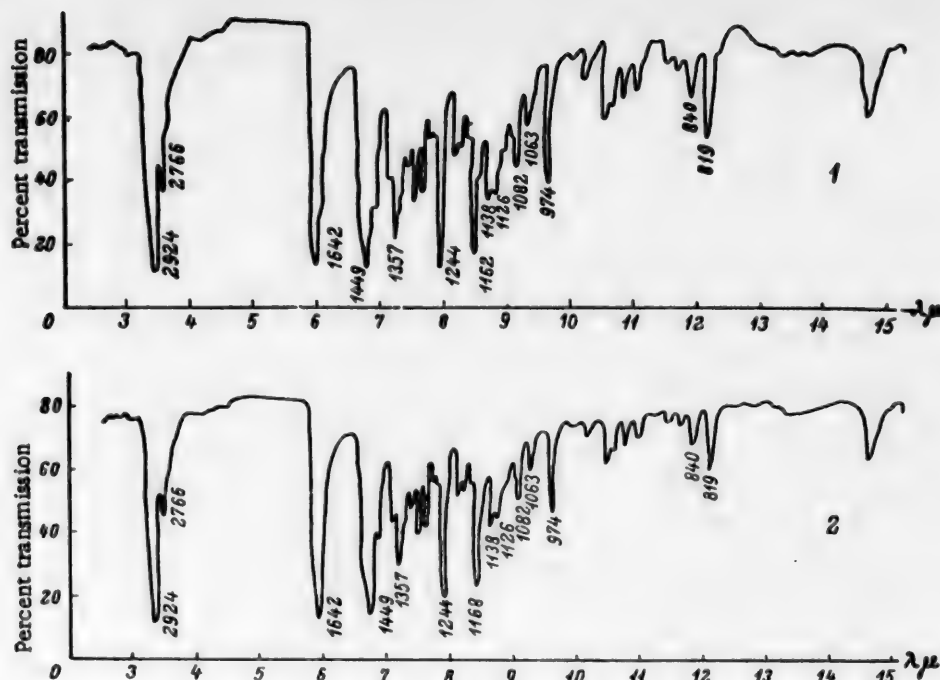
Leontine, $C_{15}H_{24}ON_2$, first isolated in 1932 by A. P. Orekhov and R. A. Konovalova from the plant *Leontice Ewersmanii* BGE [6], subsequently was investigated by Platonova and Kuzovkov [7], who, on the basis of a comparison of the products of reduction of leontine and matrine, established the affiliation of leontine to the matrine series; they explained the difference of these bases as due to the different position of the carbonyl group in their molecules, and suggested for leontine three possible formulas.

By dehydrogenation of leontine under conditions analogous to those employed by us for the dehydrogenation of matrine and sophoradine, there was obtained a product of the dehydrogenation of leontine identical to octadehydromatrine; thus it is necessary to consider leontine to be a diastereoisomer of matrine, i.e., an optical antipode of allomatrine. For confirmation of this, we obtained a racemate by mixture of leontine with allomatrine. The crystalline hydrochloride of the racemate melts at 219–220° (optically active allomatrine and leontine do not form crystalline hydrochlorides). The infrared spectra of these bases confirm their identity (see figure).

Our investigations have shown that the already known allomatrine, its antipode leontine, and sophoradine are all spatial isomers of matrine.

* ν_{\max} 1653 cm^{-1} (C=O) and 1517 cm^{-1} (C=C) in Nujol; λ_{\max}^{EtOH} $m\mu$ (log ϵ): 232 (4.023), 298–272 (3.87), 394–398 (4.024). Literature data [4]: ν_{\max} 1647 cm^{-1} (C=O) and 1518 cm^{-1} (C=C) in KBr; λ_{\max}^{EtOH} $m\mu$ (log ϵ): 230 (4.39), 270 (4.05), 3.95 (4.22).

** Employing our conditions of dehydrogenation in an experiment with matrine we achieved a significantly better yield than was reported by Kondo and Tsuda [4] for this same reaction.



Infrared spectra. 1) Allomatrine; 2) leontine.

EXPERIMENTAL

Hydrolysis of sophoradine by hydrobromic acid. Sophorodine, 1.5 g (m.p. 109-110°), was dissolved in 15 ml of 46.8% hydrobromic acid. The mixture was heated for 5 hours on a water bath and for one hour to the boiling temperature. After removal of the solvent, there remained a greasy substance, which upon the addition of small quantities of alcohol began to crystallize. There was obtained 0.76 g of the hydrobromide of sophoradinic acid with m.p. 233-234° (from alcohol).

Found %: C 41.80, 42.11; H 6.60, 6.35; N 6.53, 6.53; Br 36.42, 36.61. $\text{C}_{15}\text{H}_{26}\text{O}_2\text{N}_2 \cdot 2\text{HBr}$.
 Calculated %: C 42.06; H 6.59; N 6.54; Br 37.32.

From the mother liquor was separated 0.1 g of a substance with m.p. 236-238°.

The reduction of sophoradine by lithium aluminum hydride. A solution of 8 g of sophoradine (m.p. 109-110°) in 500 ml of absolute ether was boiled for 5 hours with 4 g of LiAlH_4 . The solution was evaporated to 100 ml, and to the remainder was carefully added 10-15 ml of water. The ether layer was separated, and the water layer was extracted with ether. From the combined ether extracts there was obtained 5.6 g of a greasy substance. Purification of the substance was carried out by distillation in vacuo at 110-134° (0.1 mm). The hydrochloride of the product of reduction was obtained, with m.p. 298-301° (from anhydrous alcohol) $[\alpha]_D -28.6^\circ$ (c 3.61, anhydrous alcohol).

Found %: C 52.45, 52.61; H 9.29, 9.21; N 8.16, 8.15; Cl 20.75, 20.61. $\text{C}_{15}\text{H}_{25}\text{N}_2 \cdot 2\text{HCl} \cdot 2\text{H}_2\text{O}$. Calculated %: C 52.47; H 9.39; N 8.15; Cl 20.65.

The base isolated from the hydrochloride of the product of reduction melted at 60-61° (from acetone), $[\alpha]_D -41.6^\circ$ (c 2.99, alcohol).

Found %: C 76.16, 77.49; H 11.10, 11.38; N 11.31, 11.60. $\text{C}_{15}\text{H}_{25}\text{N}_2$. Calculated %: C 76.86; H 11.18; N 11.95.

The base is quite soluble in ether, chloroform, acetone, alcohol, and water.

Methiodide, m.p. 301-302° (from water).

Hydrolodide, m.p. 203-205° (from water).

Dehydrogenation of sophoradine with Pd on asbestos. Sophoradine, 10 g (m.p. 108-110°), was heated with 2 g 42% Pd on asbestos for 30 minutes at 285-300° in a stream of nitrogen; there occurred during this a very energetic evolution of hydrogen. The reaction mixture after cooling was dissolved in hot acetone. The catalyst was filtered off, and the acetone was evaporated off. The crystalline residue was washed with water and afterward was extracted with a mixture of acetone and ether (1:3). Subsequent to concentration of the solution, which possessed a greenish-yellow fluorescence, a precipitate fell out, which after washing with acetone gave a substance tinged with a yellow color, with a melting point of 174-175° (literature values: 175-177°) (from acetone); $[\alpha]_D \pm 0$. The substance was readily soluble in alcohol, chloroform, and dilute mineral acids; difficultly soluble in acetone and ether.

Found %: C 74.4; H 7.0; N 11.22. $C_{15}H_{24}ON_2$. Calculated %: C 75.0; H 6.7; N 11.7.

A test mixture of the octadehydrosophoradine obtained by this method with octadehydromatrine did not give a depression of the melting point.

Dehydrogenation of matrine with Pd on asbestos. Matrine, 1.2 g, was heated with 0.28 g 42% Pd on asbestos for 30 minutes at 285-300° in a current of nitrogen. After cooling, the reaction mixture was dissolved in hot acetone, the catalyst was filtered off, and the acetone was driven off. The crystalline residue separated by suction was washed with water. The yellow, finely crystalline substance was triturated with a mixture of acetone and ether (1:3). After removal of the solvent, there was obtained 1.05 g of a substance with m.p. 165-171°. After crystallization from acetone, m.p. 174-176°.

Dehydrogenation of leontine with Pd on asbestos. Leontine, 0.5 g, was heated with 0.15 g 42% Pd on asbestos at 275-295° for 30 minutes in a current of nitrogen. The reaction mixture after cooling was subjected to extraction by hot acetone. After evaporation of the acetone there remained a yellow powdery substance which was washed first with acetone and then with ether. There was obtained 0.01 g of octadehydroleontine with m.p. 172.5-175°. Test mixtures with octadehydromatrine and octadehydrosophoradine did not give a depression of the melting point.

Formation of allomatrine.* To 2.18 g PtO_2 , reduced in 33.3 ml of glacial acetic acid, we added 2.2 g of matrine dissolved in 33.3 ml of glacial acetic acid. The reaction mixture was heated and shaken over 50 hours in an atmosphere of hydrogen. The catalyst was filtered off from the reaction mixture and the solvent completely removed. The residue was dissolved in water made alkaline with 25% KOH, and subjected to extraction with ether. After removal of the ether, the oily residue was separated through its basicity. Allomatrine was separated from the last fraction after saturation of the mother liquor with potash. We obtained 0.27 g of a substance with m.p. 102.5-106°; after purification from petroleum ether, m.p. 105-106°, $[\alpha]_D + 78.1^\circ$ (c 3.3, anhydrous alcohol). Literature data: m.p. 103-105°; $[\alpha]_D + 77^\circ$.

The formation of the racemate of allomatrine. An alcohol solution of 0.0200 g of allomatrine (m.p. 105-106°, $[\alpha]_D + 78.1^\circ$) and 0.0200 g of leontine (m.p. 106-107°, $[\alpha]_D - 78.0^\circ$) was evaporated to obtain the racemate with m.p. 86-87°, $[\alpha]_D \pm 0$.

The hydrochloride, m.p. 219-220° (from a mixture of acetone with alcohol, 1:5).

SUMMARY

1. The molecular formula of sophoradine was definitively established to be $C_{15}H_{24}ON_2$ instead of $C_{15}H_{26}ON_2$ as is given in the literature.
2. Sophoradine contains basically the matrine nucleus and is a spatial isomer of matrine.
3. Leontine is a spatial isomer of matrine, i.e., an optical antipode of allomatrine.

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* We changed the method of separating allomatrine from the reaction mixture.

THE ULTRAVIOLET ABSORPTION SPECTRA OF ALKYLIMINES OF ACETYLACETONE AND β -HYDROXYNAPHTHALDEHYDE

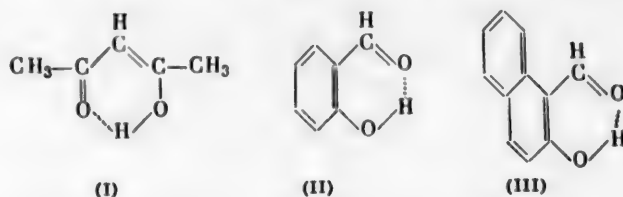
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In the absorption spectra of alkylimines of salicylic aldehyde (II) and o-hydroxyacetophenone there is an interesting effect; the occurrence in polar solvents of an intense absorption band in the region of $25,000\text{ cm}^{-1}$ [1]. Japanese investigators first found this effect which they explained by formation of hydrogen bonds [2].



Continuing the investigation of this effect, we have studied the absorption spectra of analogous systems: the alkylimines of acetylacetone (I) and β -hydroxynaphthaldehyde (III) in polar and nonpolar solvents.

Absorption Spectra of Acetylacetone Imines

In Table 1 we give the data for the absorption spectra of the acetylacetones. In Fig. 1 we give the absorption curves for acetylacetone and its methylimine. The data of Table 1 show that the solvent does not affect the spectrum of acetylacetone itself. The introduction of the alkylimino group into the acetylacetone molecule independent of the size of the alkyl radical not only does not cause the appearance of a new absorption band (as occurs in the case of salicylic aldehyde), but also does not cause any particular change in the nature of the spectrum. It should be noted that the position of the absorption maximum in the spectra of alkylimines of acetylacetone depends in some degree on the solvent; for acetylacetone imine this relationship is shown most clearly. It is probably connected with the tautomerism of these compounds which exist as enol-imines or ene-amines.

The possibility of formation of the ene-amine forms for nitrogen derivatives of acetylacetone was shown by Combes [3] who obtained acetylacetone dialkylamines by the action of secondary amines on acetylacetone. Recently Weinstein [4], using infrared spectra, showed the presence of the ene-amine structure for some acetylacetone imines.

Kochetkov and Dombrovskii, studying the molecular refraction of β -aminovinylketones, and especially methyl- β -aminovinylketone, concluded that the latter exists in the form of a tautomeric mixture of enol and ene-amine and does not contain an imine form [5]. A similar idea was expressed concerning bisacetylacetone ethylenediamine by Ueno and Martell on the basis of a study of infrared spectra [6].

Absorption Spectra of Alkylimines of β -Hydroxynaphthaldehyde

In Tables 2 and 3 we give data on the absorption spectra of alkylamines of β -hydroxynaphthaldehyde and its methyl ether; in Figs. 2 and 3 we give the characteristic spectra.

Table 3 shows that the spectrum of β -hydroxynaphthaldehyde itself, like the spectra of salicylic aldehyde, acetylacetone, and o-hydroxyacetophenone, is not changed by the influence of solvents. When we turn from β -hy

TABLE 1. Absorption Maxima of Acetylacetone Alkylimines $\text{CH}_3\text{COCH}_2\text{C}(=\text{R})\text{CH}_3$ in Different Solvents

Solvent R	Isooctane		Chloroform		Methanol		$\Delta\nu, \text{cm}^{-1}$ *
	$\nu \cdot 10^{-3} \text{ cm}^{-1}$	$\lg \epsilon$	$\nu \cdot 10^{-3} \text{ cm}^{-1}$	$\lg \epsilon$	$\nu \cdot 10^{-3} \text{ cm}^{-1}$	$\lg \epsilon$	
$=\text{O}$	36.7	3.96	36.4	3.94	36.4	3.96	300
$=\text{NH}$	35.0	4.65	34.1	4.18	33.3	4.21	1700
$=\text{NCH}_3$	33.1, 42.3	4.18, 2.75	32.2	4.27	32.2	4.37	900
$=\text{NC}_2\text{H}_5$	33.1	3.85	32.0	3.91	32.1	3.97	1000
$=\text{NC}_4\text{H}_9$	33.1	4.73	32.1	4.03	32.1	4.33	1000
$=\text{N}(\text{CH}_3)_2\text{N}-$	32.0	4.25	31.3	4.28	31.0	4.53	1000

* The shift in band of maximum absorption in methanol solution compared to the position of the maximum of the same band in isooctane solution.

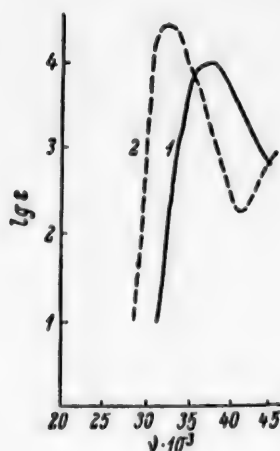


Fig. 1. Absorption spectra in methanol. 1) Acetylacetone; 2) acetylacetone methylimine.

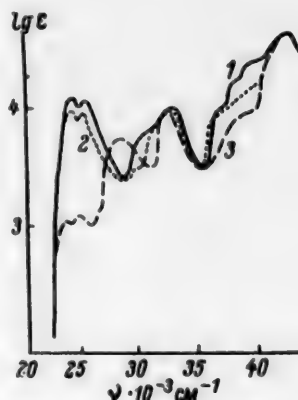


Fig. 2. Absorption spectra of the butylimine of β -hydroxynaphthaldehyde. 1) In methanol; 2) in chloroform, pyridine, and acetic acid; 3) in isooctane.

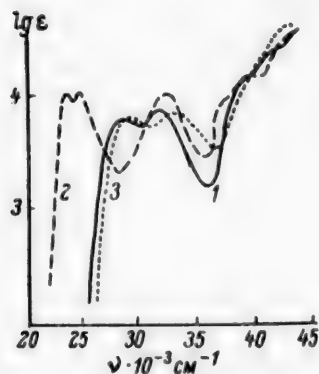
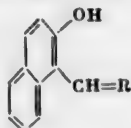


Fig. 3. Absorption spectra in methanol. 1) β -Hydroxynaphthaldehyde; 2) methylimine of β -hydroxynaphthaldehyde; 3) methylimine of β -methoxynaphthaldehyde.

droxynaphthalene to its alkylimines, a new absorption band appears in the spectra of the latter, which agrees in its position with the analogous band in the spectra of alkylimines of salicylic aldehyde. This band in the spectra of the alkylimines of β -hydroxynaphthaldehyde, as in the case of the imines of salicylic aldehyde, does not depend on the size of the alkyl radical on the nitrogen atom and is absent in the methoxy derivatives (Fig. 3). However, in distinction from the alkylimines of salicylic aldehyde, in the spectra of alkylimines of β -hydroxynaphthaldehyde the intensity of this band is not essentially changed in such solvents as methyl alcohol, chloroform, pyridine, and acetic acid. In isooctane solution the intensity of the band in the region $25,000 \text{ cm}^{-1}$ for β -hydroxynaphthaldehyde imines is decreased by the order of one, while for alkylimines of salicylic aldehyde this band vanishes entirely.

TABLE 2. Absorption Maxima of β -Hydroxynaphthaldehyde Imines in Different Solvents (In parentheses we give the maximum structural oscillation found on the basis of absorption bands)



Solvent R	Isooctane		Methanol		Chloroform		Pyridine	
	$\nu \cdot 10^{-3} \text{ cm}^{-1}$	lg ϵ	$\nu \cdot 10^{-3} \text{ cm}^{-1}$	lg ϵ	$\nu \cdot 10^{-3} \text{ cm}^{-1}$	lg ϵ	$\nu \cdot 10^{-3} \text{ cm}^{-1}$	lg ϵ
=O	27.5 (27.1, 27.9)	3.75	27.7	3.73	27.7	3.75	27.7	3.81
=NH	31.4	3.96	31.5	3.88	31.1	3.90	31.4	3.92
	25.0* (24.2, 25.6)	3.05	24.9 (24.3, 25.5)	3.85	24.6 (24.0, 25.3)	3.50	24.5 (24.0, 25.1)	3.78
	28.0	3.33						
	32.9	3.53	33.1	3.83	33.1	3.86	33.0	3.85
=NCH ₃	43.6	4.35						
	24.6 (23.8, 25.0)	3.00	24.6 (24.1, 25.0)	4.01	24.3 (24.8, 23.8)	4.04		
	28.5	3.83						
	32.3	4.08	32.7	4.02	32.3	4.15		
=NC ₂ H ₅	33.8	3.98						
	43.1	4.79			42.5			
	24.4 (23.8, 24.9)	3.15	24.7 (24.1, 25.0)	4.10	24.3 (23.8, 24.8)	4.06		
	28.3	3.86						
=NC ₄ H ₉	32.2	4.15	32.7	4.13	32.3	4.10		
	33.6	4.15						
	43.1	4.96	43.1	4.62	42.5	4.71		
	24.2	3.13	24.6 (24.1, 25.1)	4.01	24.2 (23.6, 24.8)	4.00	24.3 (23.7, 24.8)	3.95
=N(CH ₂) ₂ N=	28.0	4.00						
	32.3	4.38	32.7	4.06	32.0	4.01	32.3	4.06
	43.1	5.01						
	24.1 (23.6, 24.7)	3.89**	Not soluble					
=N(CH ₂) ₆ N=	28.5	4.25						
	31.2	4.92						
	24.1 (23.4, 24.8)	3.75	24.7 (24.7, 25.0)	4.30	24.2 (24.8, 23.6)	4.25		
	27.6	4.00						
	32.0	4.29	32.3	4.22	32.4	4.33		

* Boldface type gives the value of the maximum for the new bands which appear in the spectra of the alkylimines.

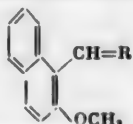
** We give data for solutions in carbon tetrachloride in view of the insolubility of the compound in isooctane.

Simultaneously with this in the spectra of alkylimines of β -hydroxynaphthaldehyde in isooctane there appears a band which is characteristic of the starting aldehyde ($28,000 \text{ cm}^{-1}$) which is not found in alcohol solutions. In isooctane

solutions on going from the corresponding alkylimines of the methyl ether of β -hydroxynaphthaldehyde to the imine of the aldehyde itself, the absorption band in the region $28,000\text{ cm}^{-1}$ was shifted in the same way as on going from the ether of β -hydroxynaphthaldehyde to the aldehyde itself.

The appearance of a supplementary absorption band in the spectra of the alkylimines of salicylic aldehyde, o-hydroxyacetophenone, and β -hydroxynaphthaldehyde in polar solvents is analogous to the effect which was described by Kiss [7] for Schiff bases of hydroxybenzaldehyde. He observed that in Schiff bases of o- and p-hydroxybenzaldehyde at the boundary of the visible field there appeared a band which was absent in the spectra of Schiff bases of m-hydroxybenzaldehyde. Kiss suggested that the appearance of this band depended either on the formation of hydrogen bonds or the occurrence of a quinone structure.

TABLE 3. Absorption Maxima for Alkylimines of β -Methoxynaphthaldehyde in Different Solvents (in parentheses we give maximum structural oscillation which is found on the basis of absorption bands)



Solvent R	Isooctane		Methanol		Chloroform		$\Delta\nu, \text{ cm}^{-1}$ *
	$\nu \cdot 10^{-3} \text{ cm}^{-1}$	lg ϵ	$\nu \cdot 10^{-3} \text{ cm}^{-1}$	lg ϵ	$\nu \cdot 10^{-3} \text{ cm}^{-1}$	lg ϵ	
$=\text{NCH}_3$	29.2 32.5 (31.9, 33.1)	3.74, 3.85	29.4 32.5 (32.2, 32.7)	3.76 3.80	28.9 32.0	3.75 3.82	700
$=\text{NC}_2\text{H}_5$	29.2 32.7 (32.2, 33.3) 42.1	3.73 3.83 4.49	29.5 33.8	3.83 3.88	29.2 33.4	3.72 3.72	900
$=\text{NC}_4\text{H}_9$	29.2 32.6	3.75 3.85	29.4 33.3 43.6	3.75 3.78 4.62			1200
$=\text{N}(\text{CH}_2)_2\text{N}=\text{}$	29.0 32.4	4.05 4.13	28.7 (27.8, 29.9) 31.9	4.43 4.23	28.2 31.8	4.17 4.16	800
$=\text{N}(\text{CH}_2)_6\text{N}=\text{}$	28.9 32.9	4.07 4.12	29.3 33.2 (33.0, 33.5)	4.08 4.10	29.2 33.6	4.03 4.05	1300

* The shift in maximum of absorption bands in the region $29,000\text{--}28,000 \text{ cm}^{-1}$ in the ether spectra with respect to the spectra of the alkylimine of β -hydroxynaphthaldehyde itself (for solutions in isooctane).

Appearance of Hydrogen Bonds in the Absorption Spectra of o-Hydroxycarbonyl Compounds

In setting ourselves the problem of the reason for the appearance of new absorption bands, we considered the question of the appearance of hydrogen bonds in the electron spectra of the corresponding carbonyl compounds. In Table 4 we give the absorption spectra of acetylacetone, salicylic aldehyde, β -hydroxynaphthaldehyde, and also their ethers in different solvents. It is evident from the table that all the compounds in which formation of hydrogen bonds is possible retain their characteristic absorption maximum and intensity in all solvents, polar and nonpolar

(isooctane, chloroform, methanol, pyridine). This can be explained by the fact that the intramolecular hydrogen bonds which are formed are so strong that they cannot be broken by formation of intermolecular hydrogen bonds under the influence of the solvent. Thus the lack of change in absorption spectra in different solvents indicates the presence of strong intramolecular hydrogen bonds, which agrees with the data in the literature [8].

Table 4 shows that in the spectrum of the methyl ethers as compared to the original hydroxycarbonyl compound there is a shift in absorption bands toward the short waves. In methyl esters in which it is impossible to have intramolecular hydrogen bonds, in distinction from the starting compounds there is a shift in absorption maxima under the influence of solvents where intermolecular hydrogen bonds are formed.

TABLE 4. Absorption Maxima of Hydroxycarbonyl Compounds and Their Ethers

Substance	Solvent		$\Delta\nu$ cm^{-1} *	Methanol, chloroform, pyridine		$\Delta\nu$ cm^{-1} *
	$\nu \cdot 10^{-3}$ cm^{-1}	$\lg \epsilon$		$\nu \cdot 10^{-3}$ cm^{-1}	$\lg \epsilon$	
Acetylacetone	36.4	3.96	} 4200	36.4	3.96	} 2800
Methyl ether of acetylacetone	40.6	4.05		39.2	4.16	
Salicylic aldehyde	30.6	3.60	} 1600	30.6	3.60	} 600
Methyl ether of salicylic aldehyde	38.7	4.05		38.7	4.05	
	32.2	3.65		31.2		
	40.3	4.00		39.3-40.0	4.07	
Hydroxyacetophenone	30.6	3.60	} 2900	30.6	3.60	} 2200
	39.3	3.95		39.5	4.00	
	39.9	4.00				
	33.5	3.45		32.8	3.55	
o-Methoxyacetophenone	41.3	3.85		40.5	3.90	
β -Hydroxynaphthaldehyde	27.1	3.75	} 800	27.7	3.75	} 400
	27.9	3.72		31.4	3.90	
	31.4	3.96				
	28.5	3.73		28.1	3.77	
β -Methoxynaphthaldehyde	31.2	3.85		31.3	3.87	

* The shift in absorption band maximum in the spectra of the methyl ethers as compared to the spectra of the original hydroxycarbonyl compounds.

The shifts which occur from formation of hydrogen bonds (difference in absorption maxima between methoxy and hydroxy compounds) depends both on the solvent and on the nature of the carbonyl compound. The greatest shift for a given compound occurs in inert solvents: thus, for acetylacetone this shift is 4200 cm^{-1} , for o-hydroxyacetophenone 2900 cm^{-1} , for salicylic aldehyde 1600 cm^{-1} , for β -hydroxynaphthaldehyde 800 cm^{-1} . In polar solvents the shift is less in size, which becomes characteristic for intermolecular hydrogen bonds of the methoxy compounds with polar solvents ($\Delta\nu$ is 2800, 2200, 600, and 400 cm^{-1} , respectively). The decreased value of the shift under the influence of formation of intramolecular hydrogen bonds in the series acetylacetone \rightarrow β -hydroxynaphthaldehyde can be explained by increase in conjugated systems and the corresponding relative decrease in importance of the contribution of the hydrogen bonds which are formed to the general energetic balance of the system [9].

It is clear from these results on the absorption spectra of systems with intramolecular hydrogen bonds that:

- 1) with the formation of intramolecular hydrogen bonds in the systems studied there is no change in the character of the spectrum, but only a shift in the absorption bands toward the long waves;
- 2) the absorption spectra of compounds with intramolecular hydrogen bonds do not change under the influence of solvents;
- 3) the size of the shift in the bands under the influence of formation of intramolecular hydrogen bonds depends on the solvent and on the nature of the compound studied and varies for these compounds within 800 to 4200 cm^{-1} (for nonpolar solvents).

The reason for the appearance in the spectra of imines of salicylic aldehyde, *o*-hydroxyacetophenone, and β -hydroxynaphthaldehyde of new absorption bands in the region of $25,000\text{ cm}^{-1}$ in polar solvents is thus not formation of hydrogen bonds, but a deeper change in the structure of the molecule. The hydrogen bonds which exist in these compounds usually cause a shift in the corresponding absorption bands in passing from the imine of a methoxy compound to the imine of the hydroxy compound itself; thus, in the imine of salicylic aldehyde for the band $31,000\text{ cm}^{-1}$, $\Delta\nu$ is 1600 cm^{-1} (isooctane); in the imine of β -hydroxynaphthaldehyde for the band $28,000\text{ cm}^{-1}$ $\Delta\nu$ is from 700 to 1300 cm^{-1} (isooctane).

Since we wished to test the second suggestion of Kiss concerning the existence of a quinoid structure for such systems, we studied the ultraviolet absorption spectra of the alkylimines of para-hydroxycarbonyl compounds. It is necessary to say that while the ortho-hydroxyalkylimines are characterized by considerable stability, their para isomers are distinguished by instability and difficulty of isolation in the pure form because of relatively rapid decomposition.

In Fig. 4 we give absorption curves for α -phenylpropylimine of *p*-hydroxybenzaldehyde* in methanol, chloroform, and isooctane.** The figure shows that, as for the ortho derivative, the spectrum of the para compound in polar solvents shows a band in the region $25,000\text{--}26,000\text{ cm}^{-1}$, whose intensity increases in going from chloroform to methanol. In isooctane solution this band is absent. Since in the para compound intramolecular hydrogen bonds are absent, the band is shifted, depending on the solvent. In the ultraviolet spectra of the alkylimines of *p*-hydroxyacetophenone, 1,4-hydroxynaphthaldehyde, and of ethylenediamine *p*-hydroxybenzaldehyde we found the same effect.

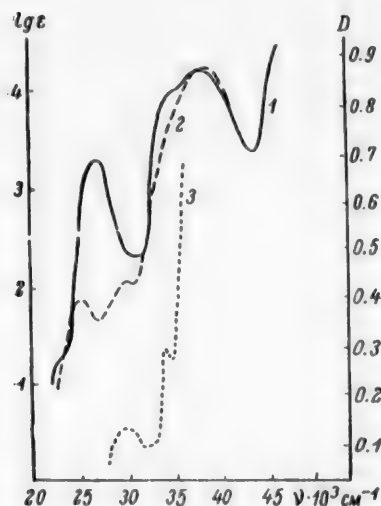
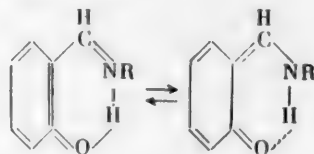


Fig. 4. Absorption spectra of α -phenylpropylimine of *p*-hydroxybenzaldehyde. 1) In methanol, ν_{\max} 26.3 ($\lg \epsilon$ 3.36); ν_{\max} 36.7–37.0 ($\lg \epsilon$ 4.32); 2) In chloroform, ν_{\max} 25.0 ($\lg \epsilon$ 1.89); ν_{\max} 30.1 ($\lg \epsilon$ 2.08); 3) in isooctane (ν_{\max} 37.7 ($\lg \epsilon$ 4.32); 3) in isooctane (scale of optical density given on the right).

the naphthalene ring, yet retains the value characteristic for benzene compounds (about $25,000\text{ cm}^{-1}$).

If we consider the above described benzene-quinoid equilibrium carefully, we can see that it is basically an enol-amine tautomerism whose presence in compounds of the aliphatic series was shown conclusively by Kochetkov and Dombrovskii [5].

Thus, for both ortho- and para-hydroxyaldehydes on passing to the nitrogen derivatives we find the same effect: the appearance of an intense absorption band in the region $25,000\text{--}26,000\text{ cm}^{-1}$. This is evidently related to formation of a quinoid structure, and hence we can suggest that in solutions of aromatic *o*-hydroxyalkylimines there is a benzene-quinoid tautomeric equilibrium.



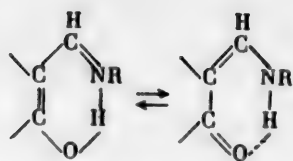
In polar solvents there is a strong shift toward the quinoid form. However, as was noted above, in *o*-hydroxyalkylimines of aromatic aldehydes there is an intramolecular hydrogen bond which is clearly shown in nonpolar solvents. The presence of this hydrogen bond determines the high stability of the ortho-hydroxy isomers as compared to their ethers and para isomers, which cannot always be isolated in an analytically pure state.

From the fact that in the spectra of alkylimines of β -hydroxynaphthaldehyde the band in the region of $25,000\text{ cm}^{-1}$ is preserved in isooctane and acetic acid solutions, and also of the slight change in intensity in other solvents, we can conclude that for the naphthalene ring the quinoid structure is more stable than for the benzene ring.

Some evidence for this is the fact that in alkylimines of β -hydroxynaphthaldehyde the position of the band which we studied, though in

* The preparation was kindly supplied by V. M. Potapov, to whom we express thanks.

** The solubility of α -phenylpropylimine of *p*-hydroxybenzaldehyde in isooctane is slight, so that its spectrum was photographed qualitatively.



Hence we can suggest that aliphatic and aromatic alkylimines tend to undergo tautomeric transformations with formation of the ene-amine form. However, formation of the ene-amine form in the aromatic system is accompanied by the appearance of a quinoid structure and its corresponding intense absorption band in the region $25,000\text{ cm}^{-1}$.

The imine-ene-amine tautomerism of a wider circle of compounds will be the subject of a later communication.

EXPERIMENTAL

Imines of Acetylacetone and Its Ether

The acetylacetone which was used as the starting material for preparing alkylimines was dried over calcined magnesium sulfate and distilled; we collected the fraction with b.p. $139-139.5^\circ$, n_D^{20} 1.4545.

The methyl ether of acetylacetone was prepared according to Eistert et al. [10]. Colorless liquid with b.p. $56-57^\circ$ (8 mm), n_D^{20} 1.4703. Literature data: b.p. $58-59^\circ$ (10 mm), n_D^{20} 1.4688 [11].

Acetylacetone imines were synthesized by one of the following methods.

a) Acetylacetone was heated on a water bath in methyl alcohol with the stoichiometric amount of amine, and in the case of acetylacetone imine and methylimine, ammonia or methylamine respectively were passed into the reaction mixture. After the solvent had been distilled off, the mixture was vacuum distilled.

b) Stoichiometric amounts of acetylacetone and the amine were heated under reflux for 2-5 hours or in a sealed tube on a boiling water bath for 3-5 hours.

The constants and analyses of the resulting compounds are given in Table 5.

TABLE 5. Alkylimines of Acetylacetone $\text{CH}_3\text{COCH}_2\text{C}(=\text{R})\text{CH}_3$

R	Meth. of prep.	Melting point	Boiling point (pressure in mm)	n_D^{20}	Empirical formula	Content of N, %		Literature reference
						found	calc.	
$=\text{NH}$	a	$42-43^\circ$	$74.5^\circ(6)$	—	$\text{C}_7\text{H}_9\text{ON}$	13.87	14.14	[14]
$=\text{NCH}_3$	a	$40.5-41$	$82-83(6)$	—	$\text{C}_8\text{H}_{11}\text{ON}$	12.25	12.40	[15]
$=\text{NC}_2\text{H}_5$	b	—	$76.5-77(10)$	1.4758	$\text{C}_9\text{H}_{13}\text{ON}$	—	—	[16]
$=\text{NC}_4\text{H}_9$	b	—	$97(4)$	1.5111	$\text{C}_{10}\text{H}_{17}\text{ON}$	8.75	9.01	
$=\text{N}(\text{CH}_2)_2\text{N}=\text{}$	b	$110-112$	—	—	$\text{C}_{12}\text{H}_{20}\text{O}_2\text{N}_2$	12.42	12.49	[3]

Alkylimines of β -Hydroxynaphthaldehyde and Its Ether

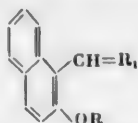
β -Hydroxynaphthaldehyde was obtained according to Russell and Lockhart [11]. The methyl ether was obtained by methylation with dimethyl sulfate [12].

Alkylimines of β -hydroxynaphthaldehyde were synthesized by one of two methods.

a) (Method of Pfeiffer, worked out for alkylimines of salicylic aldehyde [13].) We dissolved 0.02 g-mole of β -hydroxynaphthaldehyde or its methyl ether in 100 ml of methanol and added 0.02 g-mole of amine hydrochloride or 0.01 g-mole of diamine hydrochloride and twice the theoretical amount of sodium acetate. In work with the free amine, sodium acetate was not added. The reaction mixture was boiled for two hours on a water bath and water added. The crystals which precipitated were separated and purified through the hydrochloride or by recrystallization. Yield quantitative.

b) We dissolved 0.01 g-mole of β -hydroxynaphthaldehyde or its methyl ether in 30 ml of dry benzene, added a twofold excess of the amine and left it overnight. In the case of the methylimine and the imine the solution was saturated with the corresponding methylamine or ammonia, and the amine was passed until the end of the reaction. The reaction mixture was boiled in the presence of 2-3 drops of acetic acid for 6-8 hours, on which the benzene which distilled off was passed through a layer of metallic sodium for drying before returning to the reaction flask. The end of the reaction was determined by cessation of evolution of hydrogen from the sodium. The benzene was distilled off and the residue either distilled (in the case of the alkylimines of the methyl ether of β -hydroxynaphthaldehyde) or purified through the hydrochloride. Yield 40-80%.

TABLE 6. Alkylimines of β -Hydroxy- and β -Methoxynaphthaldehydes



R	R ₁	Meth. of prep.	Melting point	B. p. (pressure in mm)	n_D^{20}	Empirical formula	% N	
							found	calc.
—H	=NH	b	285—290° (decomp. ~100°)	—	—	C ₁₁ H ₉ ON	8.17, 8.15	8.18
—H	=NCH ₃	b	132—133 (from isooctane)	—	—	C ₁₂ H ₁₁ ON	7.82, 7.74	7.56
—H	=NC ₂ H ₅	a	124.5—125 (from isooctane)	—	—	C ₁₃ H ₁₃ ON	7.18, 7.22	7.03
—H	=NC ₄ H ₉	a	69.5—70 (from aqueous alcohol)	—	—	C ₁₅ H ₁₇ ON	6.08, 5.92	6.44
—H	=N(CH ₂) ₂ N=	a	311* (from nitrobenzene)	—	—	C ₂₄ H ₂₀ O ₂ N ₂	7.47, 7.49	7.60
—H	=N(CH ₂) ₆ N=	a	175 (from methanol)	—	—	C ₂₈ H ₂₈ O ₂ N ₂	6.45, 6.42	6.59
—CH ₃	=NCH ₃	b	57 (from isooctane)	170°(6)	—	C ₁₃ H ₁₃ ON	6.86, 6.85	7.03
—CH ₃	=NC ₂ H ₅	b	44.5 (from isooctane)	165—165.5 (3—4)	1.6311	C ₁₄ H ₁₅ ON	6.57, 6.46	6.57
—CH ₃	=NC ₄ H ₉	b	—	176 (3—4)	1.6095	C ₁₆ H ₁₉ ON	5.74, 5.69	5.80
—CH ₃	=N(CH ₂) ₂ N=	a	145—146 (from aqueous methanol)	—	—	C ₂₆ H ₂₄ O ₂ N ₂	6.95, 7.03	7.07
—CH ₃	=N(CH ₂) ₆ N=	a	132—132.5 (from aqueous methanol)	—	—	C ₃₀ H ₃₂ O ₂ N ₂	6.12, 5.87	6.19

* Described by P. Pfeiffer; m.p. 311° [13].

The imine, methylimine, ethylimine, and butylimine of β -hydroxynaphthaldehyde were purified through the hydrochloride as follows: the reaction product was dissolved in dilute hydrochloric acid, filtered, and the mixture then extracted with ether. The purified solution was carefully neutralized with a dilute solution of potash under an ether layer. The imine which precipitated was quickly extracted with ether and after distillation of the ether was recrystallized. The constants and analyses of the resulting compounds are given in Table 6.

The absorption spectra were taken on an SF-4 spectrophotometer.

SUMMARY

1. We have taken the ultraviolet absorption spectra of alkylimines of acetylacetone and β -hydroxynaphthaldehyde in different solvents.

2. For the alkylimines of β -hydroxynaphthaldehyde we have found, as for the corresponding benzene derivatives, the occurrence of an absorption band in the region $25,000\text{ cm}^{-1}$ whose intensity is not changed in such polar solvents as methanol, chloroform, pyridine, and acetic acid, and is lowered by an order of one in nonpolar solvents.

3. Analogous absorption occurs in the corresponding para isomers.

4. For aromatic o-hydroxycarbonyl compounds the position of the band in the region $25,000\text{ cm}^{-1}$ corresponds to formation of a quinoid structure, and the occurrence in the compounds studied of a hydrogen bond assures great stability for the ortho isomers.

5. It is established that for o-hydroxyalkylimines of aromatic aldehydes there is a benzene-quinoid equilibrium which is a special case of an enol-amine tautomeric equilibrium.

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THE STRUCTURE OF PRANGENINE

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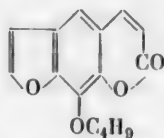
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We have previously reported [1] on the furocoumarin prangenine (m.p. 96.5-97°) isolated from the resin of the root of *Prangos pabularia* L. Prangenine was assigned the formula $C_{15}H_{14}O_4$ and the suggested structure was that of a butyl ether of xanthotoxol [2,3]. However, the structure of the side chain remained unsettled.



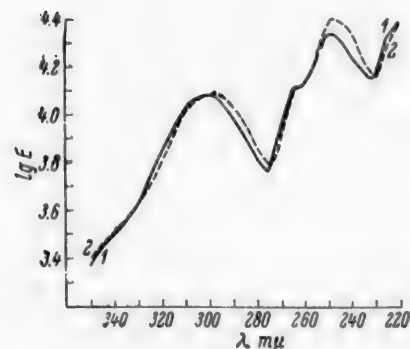
It was also suggested in the literature [4] that prangenine was identical with imperatorine, a furocoumarin isolated from the root of *Imperatoria ostruthium*.

In undertaking a more detailed study of the structure of prangenine, since we knew the difficulty of separating and purifying the furocoumarins by crystallization, we decided to use a chromatographic method.

By the method of adsorption chromatography on aluminum oxide we were able to separate prangenine into two substances. When we eluted with a mixture of chloroform and ligroin we isolated from the first fraction a substance (I) with m.p. 99.5-100.5°, and from later fractions a substance (II) with m.p. 113-114.5°.

By the method of descending paper chromatography we showed that both substances give a spot with a yellow fluorescence in ultraviolet light and differ sharply in R_f values. Substance (I) has R_f 0.70-0.78, substance (II), R_f 0.30-0.32.

The ultraviolet spectra of both substances are very similar: The positions of the maximum absorption band are close (249 and 300, and 248 and 200 mμ, respectively), but the bands differ somewhat in intensity (see figure).



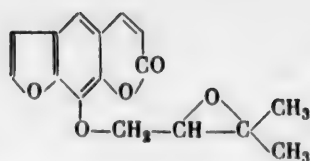
Ultraviolet absorption spectra. 1) Imperatorine; 2) prangenine.

From the results of elementary analysis, substance (I) has the composition $C_{16}H_{14}O_4$, and from its melting point it is imperatorine. A sample mixed with imperatorine* gave no depression of the melting point.

Confirmation of the identity of substance (I) and imperatorine was obtained by preparing alloimperatorine with m.p. 228° when substance (I) was distilled in a vacuum.

Substance (II) with m.p. 113-114.5° is pure prangenine. On the basis of the results of elementary analysis and molecular weight we suggest for prangenine the formula $C_{16}H_{14}O_5$ instead of our earlier formula $C_{15}H_{14}O_4$. The new molecular formula of prangenine agrees with the formula of an oxide of imperatorine.

*Imperatorine was kindly supplied to us by Yu. A. Dranitsyna, who isolated it from the fruit of *Archangelica decurrens* Ldb.



The melting point of prangenine (114.5°) is close to the melting point of the oxide of imperatorine (115-116°) obtained by Späth and Holzen [5]. A sample of a mixture of prangenine with a known imperatorine oxide prepared by us gave no melting point depression. The identity of prangenine with the imperatorine oxide was also confirmed by the agreement of the R_f values of both preparations and the sameness in character of the luminescence of their spots on the chromatogram in ultraviolet light.

Hence we can consider it established that prangenine is identical with imperatorine oxide, which is thus a natural furocoumarin.

EXPERIMENTAL

Chromatography of prangenine. A column (diameter 25 mm, height 270 mm) was filled with Al_2O_3 (30 g, 3rd activity according to Brockman) and moistened with ligroin (b.p. 40-50°). Through the column was passed a solution of 0.6 g of prangenine (m.p. 95-96°) in a mixture of chloroform and ligroin (1:2). Elution was carried out with a mixture of chloroform and ligroin in the ratios 1:5 and 1:2. The volume of each fraction was 15 ml. Results of the chromatography are given in the table.

Chromatography of Prangenine (Ratio of chloroform and ligroin)
in the eluting mixture 1:5 for fractions 1-18, and 1:2 for fractions 19-20)

Fraction No.	Wt. of eluted substance, in mg	Melting point	No. of spots on chromatogram	R_f
1	—	—	—	—
2	100	99-99.5°	1	0.70-0.78
3	200	99.5-100.5	1	
4	50	99.5-100.5	1	
5	Trace	—	2	0.70, 0.30
6	"	—	2	
7	"	—	2	
8	"	—	2	
9	"	—	2	
10	"	—	2	
11	"	—	2	
12	"	—	2	
13	"	—	2	
14	"	—	2	
15	"	—	2	
16	40	111.5	1	0.30
17	50	113.0	1	0.30
18	50	114.5	1	0.30-0.32
19	100	114.5	1	
20	10	114.5	1	

The substances with m.p. 99.5-100.5° and 113-114.5° were chromatographically pure, since they gave one spot in paper chromatography. The paper chromatogram was obtained in a pyridine atmosphere, where the non-mobile phase was ethylene glycol and the mobile phase was benzene [6].

Substance (I) (m.p. 99.5-100.5°, imperatorine)

Found %: C 71.00, 70.83; H 5.45, M 255. $C_{25}H_{14}O_4$. Calculated %: C 71.11; H 5.18. M 270.

Substance (II) (m.p. 114.5°, prangenine)

Found %: C 67.09, 67.04; H 4.91, H 4.99, M 270, 264. $C_{25}H_{14}O_5$. Calculated %: C 67.13; H 4.93, M 236.

Preparation of imperatorine oxide. One g of imperatorine was dissolved in 5 ml of chloroform; 50 ml of a chloroform solution of benzoyl peroxide (1 g) was added, and the solution stood for five days at room temperature. Then it was diluted with a large volume of ether (300 ml) and shaken with 10% K_2CO_3 solution. The ether-chloroform solution was concentrated in a vacuum and passed through Al_2O_3 (15 g). In the elution we obtained imperatorine oxide with m.p. 114° and R_f value 0.32. The luminescence of the spot on the paper chromatogram in ultraviolet light was yellow.

Found %: C 67.24; 67.36; H 5.08, 5.05. $C_{25}H_{14}O_5$. Calculated %: C 67.13; H 4.93.

A sample of a mixture of imperatorine oxide and substance (II) gave no melting point depression. The R_f value and yellow luminescence of the spot on the chromatogram in ultraviolet light were the same for both substances.

SUMMARY

1. Chemically and chromatographically pure prangenine from the root secretion of *Prangos pabularia* has the composition $C_{25}H_{14}O_5$ and m.p. 114.5°.
2. It was found that prangenine is identical with imperatorine oxide.
3. It was established that in the root secretion of *Prangos pabularia* besides the earlier discovered oxypeucedanin and osthole there are also imperatorine and imperatorine oxide (prangenine).

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PYRIDINE-CUPROUS CHLORIDE COMPLEX AS A CATALYST FOR AUTOOXIDATION

II. AUTOOXIDATION OF AMINES DEPENDING ON SUBSTITUENTS IN THE AROMATIC RING

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In a previous communication [1] we described the preparation of azo compounds by oxidation of some primary aromatic amines by gaseous oxygen in the presence of the catalyst $\text{Cu}_2\text{Cl}_2 \cdot 6\text{C}_5\text{H}_5\text{N}$. On further study of this reaction it was shown that the rate and character of the oxidation in aniline derivatives depended largely on the nature of the amine. Thus, while aniline, p-toluidine, and p-anisidine were converted very rapidly into the corresponding azo compounds, m-nitroaniline was very difficult to convert by oxidation under these conditions, and p-nitroaniline, anthranilic acid, and methyl anthranilate scarcely reacted at all. It was therefore interesting to study the comparative rates of oxidation of different amines on the rate of absorption of oxygen.

We carried out the experiments in the apparatus described earlier which we used for determining the amount of oxygen absorbed by the catalyst [1]. The volume of oxygen absorbed was determined each five minutes. For comparison the values of this volume were calculated in percent of the theoretical volume calculated under these conditions, that is, the volume needed for full dehydrogenation of the given amount of amine with account of the volume absorbed by the catalyst [1].

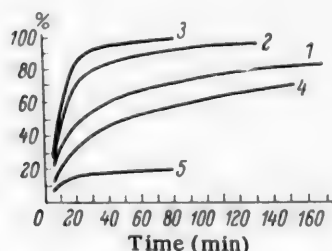


Fig. 1. Relation of rate of autooxidation to nature of amine. 1) Aniline; 2) p-toluidine; 3) p-anisidine; 4) m-xylidine; 5) m-nitroaniline.

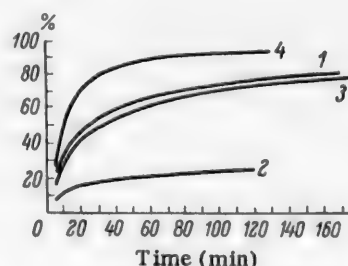


Fig. 2. Comparative rates of autooxidation of the toluidines. 1) Aniline; 2) o-toluidine; 3) m-toluidine; 4) p-toluidine.

Figure 1 shows the relation of rate of absorption of oxygen to nature of the amine. In Figs. 2, 3, 4, and 5 are the respective separate presentations of the results of experiments with all three isomers of the toluidines and chloro-, bromo-, and iodoanilines (in each figure, for comparison, we give the curve of oxidation of aniline). The reaction rate was very considerable in p-toluidine, and especially in p-anisidine; in the haloanilines it was much lower, and entirely inappreciable in m-nitroaniline; p-nitroaniline did not absorb oxygen at all. These effects of substituents can be explained by inductive effects. Since the essence of the oxidation process here is the giving up of electrons and protons, nucleophilic groups should aid it and electrophilic groups should hinder it. Thus, nitro groups almost completely suppress the oxidation, and methyl and especially methoxy groups permit the process to a large extent.

The position of the substituent is also in great degree reflected in the course of the reaction, as can be seen in the comparative curves in Figs. 2-5. The greatest rate occurs in the para isomers, markedly less in the meta isomers,

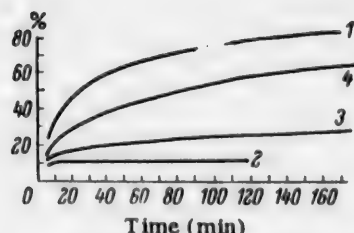


Fig. 3. Comparative rates of autooxidation of the chloroanilines. 1) aniline; 2) o-chloroaniline; 3) m-chloroaniline; 4) p-chloroaniline.

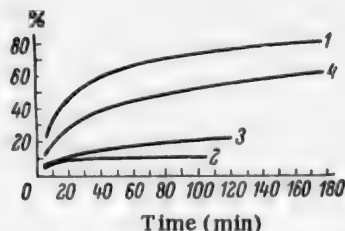


Fig. 4. Comparative rates of autooxidation of the bromoanilines. 1) Aniline; 2) o-bromoaniline; 3) m-bromoaniline; 4) p-bromoaniline.

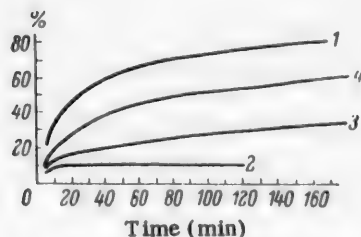


Fig. 5. Comparative rates of autooxidation of the iodoanilines. 1) Aniline; 2) o-iodoaniline; 3) m-iodoaniline; 4) p-iodoaniline.

dation of phenylhydroxylamine to nitrosobenzene is considerably greater than the rate of its condensation, and the nitrosobenzene, not finding phenylhydroxylamine in the reaction mixture, combines with unreacted amines to give azo compounds.

To test this idea under our conditions, we carried out the oxidation of phenylhydroxylamine in pyridine solution in the presence of Cu_2Cl_2 with consideration of the rate and volume of oxygen absorption. It was shown that although phenylhydroxylamine is oxidized very rapidly under these conditions (the reaction was complete in 15-20 minutes), yet condensation with its oxidation product, nitrosobenzene, occurs still more rapidly. This is shown by the fact that oxygen is absorbed in an amount sufficient for oxidation of only half the amount of phenylhydroxylamine taken, and the second half of the latter is condensed with the nitrosobenzene which is formed to give azoxybenzene, obtained in quantitative yield. In another experiment where we took a mixture of phenylhydroxylamine and nitrosobenzene in equivalent amounts, only 15% of the phenylhydroxylamine was oxidized, and the rest during the experiment was condensed with the nitrosobenzene. We could not isolate an appreciable amount of azobenzene as a result of a direct experiment when a mixture of aniline, nitrosobenzene, pyridine and cuprous chloride stood for a day in a hydrogen atmosphere.

and in the ortho isomers absorption of oxygen is scarcely found. It can be assumed that this peculiar "ortho effect" is explained by the formation of hydrogen bonds between the amino groups and the atom of substituent in the ortho position.

It is important to note that under the conditions which we studied, only primary aromatic amines were oxidized. The secondary fatty-aromatic amine N-ethylaniline was not changed; in the same way there was no oxidation of primary aliphatic amines, isomylamine and p-methoxybenzylamine.

For comparison we carried out under the same conditions the oxidation of hydrazo compounds. The kinetics of oxidation of hydrazo compounds are shown in Fig. 6. We see that hydrazo compounds under these conditions are oxidized very energetically; the process is complete in 15-20 minutes, which is considerably faster than for the corresponding amines, as can be seen immediately by comparing Figs. 1 and 6. It is also characteristic for the hydrazo compounds that the nature of the aryl group has almost no effect on the rate of the process, from which we can conclude that oxidation in the hydrazo compounds takes place by another mechanism than with the amines.

Mechanism of the reaction. There are two main points of view as to the question of the reaction mechanism of the oxidation of the amines, those of Bamberger [2] and Goldschmidt [3].

According to Bamberger, the main direction is expressed by the following scheme.



As a result of branching, condensation, and further oxidation various products are obtained. This, for example, condensation of phenylhydroxylamine with nitrosobenzene gives azoxybenzene.



The formation of azobenzene is explained by Bamberger by the reaction of nitrosobenzene with unchanged amine.

In our experiments we never succeeded in finding even traces of azoxy compounds among the reaction products. According to Bamberger, this can be explained by the fact that the rate of oxidation of phenylhydroxylamine to nitrosobenzene is considerably greater than the rate of its condensation, and the nitrosobenzene, not finding phenylhydroxylamine in the reaction mixture, combines with unreacted amines to give azo compounds.

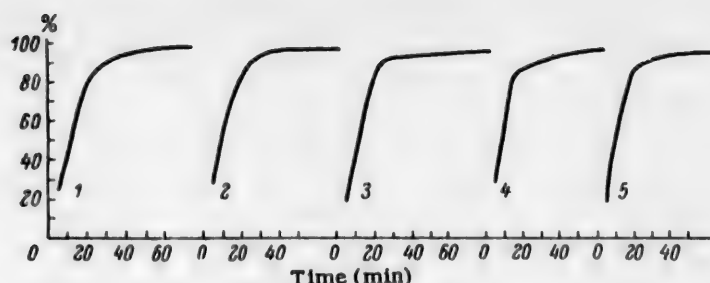


Fig. 6. Comparative rates of autooxidation of hydrazo compounds. 1) 3,3'-Dinitrohydrazobenzene; 2) 4,4'-dimethoxyhydrazobenzene; 3) hydrazobenzene; 4) 4,4'-hydrazo-m-xylene (2,4,2',4'-tetramethylhydrazobenzene), 5) 4,4'-dimethylhydrazobenzene.

We can conclude from the above that in this reaction the path to azo compounds which are obtained in a number of cases with yields nearly quantitative does not lie through phenylhydroxylamine; that is, the scheme of Bamberger is not used here.

We proceed to explain the mechanism of the reaction by the theory of Goldschmidt according to which at the basis of the various products of most of the reactions of oxidation of the amines lie the radicals ArN^\bullet or ArNH^\bullet , which result from dehydrogenation of the amino group.

We suggest that the process in this case goes by the following scheme:



The fact that hydrazo compounds were not observed by us among the reaction products is quite natural, since they are oxidized very rapidly.

We consider that the dehydrogenation in this case goes to the stage ArNH^\bullet and not ArN^\bullet on the basis of the following considerations: it would be difficult to explain the almost exclusive formation of azo compounds starting from the radical ArN^\bullet , for in this case we would expect more varied products (phenyl quinone imide, emeraldine, etc.); also, removal of the second hydrogen atom is evidently more difficult and requires more severe conditions of oxidation. Actually, carrying out the reaction with heat and in concentrated solutions leads to formation of a considerable amount of amorphous product which is evidently based on the radical ArN^\bullet . The great difficulty in removing the second hydrogen atom can be explained by the fact that N-ethylaniline does not undergo oxidation under these conditions.

EXPERIMENTAL

Experiments on determining the relative rate of oxidation of different amines. For each experiment we took 0.006 g-mole of amine, 1.16 g Cu_2Cl_2 , and 10 ml of pyridine. Shaking the flask was continued until oxygen absorption became very slow (to 0.2 ml in 5 minutes). Then the flask remained connected with the buret until the next day (a rather small amount of oxygen was then absorbed). On the next day we isolate the products as follows: to the contents of the flask we added hydrochloric acid, and the precipitated azo compound was sucked off, washed on the funnel, dried in a drying oven or desiccator, and weighed. For final purification the azo compound was recrystallized from a suitable solvent. The results of the experiments are given in the table.

Azo compounds were not isolated in the case of the ortho isomers of the above amines, where oxygen absorption was very slight.

Experiments on explaining the mechanism of the reaction. a) In the flask of an apparatus for calculating the rate and amount of oxygen absorption was placed 0.65 g (0.006 g-mole) of freshly prepared phenylhydroxylamine, 0.16 g of Cu_2Cl_2 , and 10 ml of pyridine. Oxygen absorption stopped after 20 minutes, in the course of which 46 ml of O_2 (748 mm, 15°) was absorbed. After subtracting the 9.8 ml absorbed by the Cu_2Cl_2 , 36.2 ml of O_2 were used up on the phenylhydroxylamine. We calculated for complete oxidation to nitrosobenzene 73.2 ml of O_2 .

Results of Experiments on Autooxidation of Amines

Amine	Amount of amine (in g)	Yield of azo compound		Melting point	
		(in g)	(in %)	after one re-crystallization	according to literature
Aniline	0.56	0.49	89	68°	68° [4]
p-Toluidine (monohydrate)	0.75	0.6	95.4	144	144 [4]
m-Toluidine	0.64	0.45	70	54	54 [4]
p-Anisidine	0.76	0.68	93	162	164 [5]
m-Xyldine	0.73	0.5	68.5	129	129 [4]
p-Chloroaniline	0.76	0.55	73.3	187	188 [6]
m-Chloroaniline	0.76	0.2	26.3	101	101 [4]
p-Bromoaniline	1.03	0.76	74.5	205	205 [4]
m-Bromoaniline	1.03	0.3	29.4	125	126 [7]
p-Iodoaniline	1.31	0.9	69.2	237	237 [7]
m-Iodoaniline	1.31	0.5	30.8	149	150 [7]
m-Nitroaniline	0.83	0.1	12.2	153	153 [8]

The reaction mass was acidified with HCl and extracted with ether. The ether extract was dried over CaCl_2 . After distillation of the ether, an oil remained which quickly solidified to a yellow, crystalline mass (0.6 g) with m.p. 34°. After recrystallization from methanol, light-yellow needles with m.p. 36° (azoxybenzene).

b) The experiment was repeated with twice the amount of phenylhydroxylamine used in the previous experiment (1.3 g). There was absorption of 81.5 ml of O_2 (748 mm, 15°). On the Cu_2Cl_2 was used 9.8 ml; hence the $\text{C}_6\text{H}_5\text{NHOH}$ absorbed 71.7 ml. The calculated value was 146.4 ml. of O_2 .

c) We took 1.3 g (0.012 g mole) of phenylhydroxylamine, 1.28 g (0.012 g mole) of nitrosobenzene, 0.16 g of Cu_2Cl_2 , and 10 ml of pyridine. Thirty-two ml of O_2 was absorbed (750 mm, 15°). Cu_2Cl_2 used 9.8 ml. $\text{C}_6\text{H}_5\text{NHOH}$ absorbed 22.2 ml of O_2 , or 15% of the theoretical amount.

By steam distillation we recovered from the reaction mass 0.2 g of unreacted nitrosobenzene, and from the residue after treatment as before we obtained 2 g of azoxybenzene.

d) In a 50-ml flask from which air was removed by an energetic stream of hydrogen we placed 2 g of nitrosobenzene, 2 g of aniline, 20 ml of pyridine, and 0.2 g of Cu_2Cl_2 . Immediately after mixing, the color became dark brown. Hydrogen was passed for 15 minutes more; then the flask was tightly closed with a rubber stopper and left until the next day. The reaction mass was acidified with hydrochloric acid and extracted with ether. The residue after distillation of the ether was steam distilled. First nitrosobenzene distilled in the amount of 0.8 g; then 0.5 g of orange-yellow crystals distilled, melting over a wide range (25-40°). A considerable amount of tarry residue remained in the flask. Repeated recrystallizations of the crystalline substance from methanol gave a small fraction with m.p. 30-33°. Complete separation of the mixture was not successful.

SUMMARY

1. We have studied the relative rates of oxidation of a number of aromatic amines by gaseous oxygen in the presence of the pyridine-cuprous chloride complex as a catalyst. We have showed a marked relation of the rate of the reaction to the nature and position of substituents in the aromatic ring.

2. We have found that primary aliphatic amines and also N-alkyl substituted aromatic amines are not oxidized under these conditions. Hydrazo compounds are energetically oxidized to the corresponding azo compounds. Phenylhydroxylamine is equally rapidly oxidized, giving quantitative yields of azoxybenzene.

3. We have showed that the mechanism of Bamberger does not explain the formation of azo compounds under these conditions. We suggest that the latter are formed through intermediate $\text{ArNH}\cdot$ radicals, which dimerize into hydrazo compounds with later oxidation to azo compounds.

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A NEW VARIANT OF THE AMINE METHOD FOR THE SYNTHESIS OF FERROCENE

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Original article submitted February 4, 1960

Of the many methods for obtaining ferrocene the most interesting is the so-called "amine method" suggested by Wilkinson [1,2] in which ferrocene is obtained by condensation of cyclopentadiene with FeCl_2 in the presence of organic bases (diethylamine).



The amine method is distinguished by its simplicity and the high yield of desired product (84-88%). In this method it is recommended to use FeCl_2 in the active form by reduction of FeCl_3 with powdered metallic iron (finely ground) with heating in a medium of tetrahydrofuran or the dimethyl ether of ethylene glycol [3].

By observing all the conditions of Wilkinson we obtained ferrocene by the amine method (in tetrahydrofuran) with a yield of 61%; we did not get a yield of 84-88% apparently because we used a starting material with a different degree of purity.

We obtained higher yields of ferrocene by the amine method (65%) by using butyl acetate instead of tetrahydrofuran (with equal volume).

In order to simplify the method of obtaining ferrocene, we used the information in patents for obtaining FeCl_2 , which consists in heating FeCl_3 with chlorobenzene at about 140° [4]. We showed that this method leads to obtaining FeCl_2 which is fully active in the reaction of condensation with cyclopentadiene in the presence of diethylamine.

Summarized Table of Experiments on the Ferrocene Synthesis

Solvent for FeCl_3	Base	Yield of ferrocene, %
A. Experiments with reduction of FeCl_3 by metallic iron		
Tetrahydrofuran	Diethylamine	61.0
Butyl acetate		65.0
Ethyl butyrate		54.5
Di-n-butyl ether		42.2
Anisole		40.0
Phenetole		38.0
Methylisobutyl ketone		27.0
Dioxane		15.2
Diisoamyl ether		10.8
Tetrahydrofuran	Triethylamine	6.0
Butyl acetate		5.3
Butyl acetate	Sodium ethylate	0
B. Experiments with preliminary reduction of FeCl_3 by chlorobenzene		
Not required	Diethylamine	66.0
	Triethylamine	14.1
	Pyridine	0

For satisfactory comparison of the final results all the experiments were carried out with the same amounts of reagents (see summarized table). The yield of ferrocene was calculated on the iron.

As the data in the table show, good enough results in the experiments of series A were obtained using as the solvent ethers (di-n-butyl ether, anisole, phenetole) and esters (ethyl butyrate and butyl acetate).

In pyridine, anhydrous alcohol, and acetone, reduction of FeCl_3 to FeCl_2 under the influence of metallic iron did not occur. If instead of acetone we used methylisobutylketone, we could obtain a yield of 27% ferrocene.

Attempts to replace diethylamine in the second stage of the synthesis by triethylamine, pyridine, or sodium ethylate did not succeed. Below we give a description of the method recommended for the synthesis of ferrocene.

EXPERIMENTAL

In a 0.5-liter round-bottomed flask fitted with a reflux condenser and a tube for adding nitrogen was placed 43.0 g (0.25 g-mole) of FeCl_3 (anhydrous) and 53 ml (0.5 g-mole) of chlorobenzene. The reaction mixture was heated in an atmosphere of dry nitrogen for two hours at 140° (thermometer in the oil bath). At the end of the reaction reduction was estimated by stoppage of weight gain of the flask with the alkaine solution in which the gaseous hydrogen chloride formed in the reaction was absorbed. The FeCl_2 which was formed was separated on a Buchner funnel and washed with absolute diethyl ether in an atmosphere of dry nitrogen. The light-gray crystalline powder of FeCl_2 was transferred to a reaction flask fitted with a stirrer, reflux condenser, and dropping funnel, and to it with effective stirring in an atmosphere of dry nitrogen was added a solution of 42 ml (0.5 g-mole) of cyclopentadiene in 100 ml of diethylamine. After three-hour stirring, ferrocene was distilled from the reaction mixture with superheated steam.

SUMMARY

1. We have showed that in the synthesis of ferrocene by the amine method, tetrahydrofuran used as the solvent in the reduction of FeCl_3 can successfully be replaced by esters: ethyl butyrate and butyl acetate. The best yield was obtained with butyl acetate (65%).

2. We have showed that the use of such organic bases as triethylamine, pyridine, and sodium ethylate for the condensation instead of diethylamine results in a sharp fall in yield of ferrocene.

3. We have worked out a simpler variant of the amine method for obtaining ferrocene, including the preliminary reduction of FeCl_3 by chlorobenzene.

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AMINOCOLCHICIDE AND ITS DERIVATIVES

III. COLCHICIDE DERIVATIVES OF GLYCINE AND β -ALANINE

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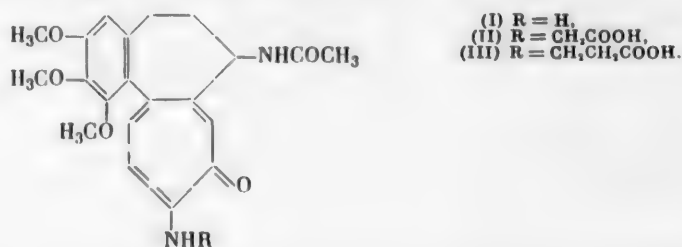
pp. 334-335, January, 1961

Original article submitted February 11, 1960

The reaction of colchicine and ammonia with formation of aminocolchicide* (I) was discovered by Zelsel [1]. Then it was shown that not only ammonia could react thus, but also various aliphatic and heterocyclic primary and secondary amines [2-10]. Exchange of a mobile methoxy by an amino group occurs in other alkaloids of the colchicine group [11-18] and also in their derivative [6,12,19-22].

We have assumed that in the reaction of colchicine with amino acids we can also obtain N-colchicide derivatives of amino acids. For preliminary experiments we have chosen amino acids in which there is no asymmetrical carbon atom, glycine and β -alanine.

Amines react with colchicine alkaloids in ratios of 1.5 to 8 moles of amine per 1 mole of alkaloid [2-6,8-9, 13-15, 17]. For amino acids such an excess is not enough: colchicine reacts completely in the presence of 15-20 moles of amino acids. It was also shown that alkali had to be present. N-Colchicidyl glycine (II) and N-colchicidyl- β -alanine (III) were obtained in yields of about 83%.



With a smaller excess of amino acids some of the colchicine did not react, and without alkali the reaction did not take place, and colchicine was recovered almost completely.

The positive effect of alkali is not unexpected, since alkali binds the carboxyl of the amino acids and thus liberates the amino group, which in the free amino acids, as is known, takes part in the formation of zwitter ions [23].

We express thanks to L. M. Utkin for interest in this work.

EXPERIMENTAL

Ten g (1 $\frac{1}{2}$ mole) of colchicine (containing $\frac{1}{2}$ mole of ethyl acetate of crystallization [24]) in 25 ml of alcohol was mixed with a water solution of amino acid and 16 g (17.7 $\frac{1}{2}$ moles) of sodium hydroxide. A yellow color quickly developed and grew stronger with standing. The solution was kept at room temperature for two days and was treated with 1.0 g of activated charcoal (alkaline, variety AO).

N-Colchicidyl glycine (II). We took 31.0 g of glycine (18.2 $\frac{1}{2}$ moles) in 350 ml of water. The filtered solution which contained the reaction product was acidified with hydrochloric acid to a weakly acid solution to Congo. The precipitate was exhaustively extracted with chloroform. From the extract we obtained a yellow, tarry residue which crystallized after treatment with 30 ml of acetone. We obtained 9.32 g of a yellow, crystalline substance. Recrystal-

* This name [2] seems to us more suitable than others used in some cases.

\dagger As in original—Publisher.

lization from a mixture of acetone and alcohol gave 8.39 g (83.6%) of N-colchicidyl glycine (II) with m.p. 226-227° (decomposition), $[\alpha]_D^{22} - 236.2^\circ$ ($c = 0.479$, alcohol). Substance (II) was easily soluble in alcohol and chloroform, somewhat less so in methanol, difficultly so in acetone and water, easily soluble in a water solution of sodium bicarbonate.

For analysis it was dried for six hours at 100° and 3 mm.

Found %: C 61.93, 62.03; H 6.01, 5.98; N 6.12, 6.36; OCH_3 20.05. $\text{C}_{23}\text{H}_{35}\text{O}_7\text{N}_2$. Calculated %: C 62.41; H 5.92; N 6.34; OCH_3 21.05.

N-Colchicidyl- β -alanine (III). We took 36.0 g of β -alanine (17.9° moles) in 300 ml of water. After filtration the solution which contained the reaction product (III) was acidified with hydrochloric acid to about pH 4. The yellow precipitate was filtered off and washed with water. Weight 9.19 g, m.p. 160-162°, $[\alpha]_D^{22} - 222.5^\circ$ ($c = 0.687$, alcohol). The mother liquor was exhaustively extracted with chloroform. The residue after distillation of the chloroform weighed 1.31 g. For purification the substance was reprecipitated from a soda solution by acidification with hydrochloric acid to about pH 4. We obtained 8.63 g of substance which contained 1 mole of water of crystallization. Yield 78.6%, m.p. 162-165° (in a capillary) and 159-160° (on a Koffler block), $[\alpha]_D^{22} - 225.5^\circ$ ($c = 0.713$, alcohol). The substance was easily soluble in alcohol, chloroform, methanol and acetone, difficultly so in water, soluble in a water solution of sodium bicarbonate.

For analysis it was dried over phosphoric anhydride for ten hours at 100° and 2 mm.

Found %: N 6.13, 5.93; OCH_3 19.65, 20.03. $\text{C}_{24}\text{H}_{28}\text{O}_7\text{N}_2$. Calculated %: N 6.14; OCH_3 20.40.

Found %: H_2O 3.90. $\text{C}_{24}\text{H}_{28}\text{O}_7\text{N}_2 \cdot \text{H}_2\text{O}$. Calculated %: H_2O 3.80.

The mother liquor after separation of the colchicide derivatives of the amino acids could be used for further preparation of these products.

SUMMARY

We have obtained N-colchicidyl derivatives of glycine and β -alanine, which shows the possibility of reaction of colchicine with amino acids as in the reaction with ammonia.

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* As in original—Publisher.

LETTER TO THE EDITOR

ALKYLATION BY ESTERS OF CARBOXYLIC ACIDS WHICH CONTAIN FLUORINE

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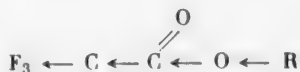
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 1,

pp. 336-337, January, 1961

Original article submitted July 28, 1960

In the literature there is a description of the preparation in small yield of 2,4-dichlorophenoxydifluoroacetic acid in the reaction of sodium 2,4-dichlorophenolate and methyl chlorodifluoroacetate [1]. We decided to extend this reaction to other phenols and thiophenols. However, in the reaction of dry sodium p-chlorothiophenolate with methyl chlorodifluoroacetate we obtained a yield of 80% of p-chlorophenylmethyl sulfide. Its structure was shown by oxidation to the sulfone with m.p. 95-96°. A sample mixed with the sulfone obtained by oxidation of pure p-chlorophenylmethyl sulfide gave no melting point depression. When sodium phenolate was heated with methyl chlorodifluoroacetate we obtained anisole in about the same yield. Thus we showed the possibility of alkylation of esters of carboxylic acids. We also carried out the reaction of sodium p-chlorothiophenolate with ethyl trifluoroacetate. Here we obtained p-chlorophenylethyl sulfide.

As is known, the ability to cause alkylation is possessed only by esters of strong inorganic acids. Esters of carboxylic acids are not alkylating substances. However, the introduction of atoms of fluorine into the molecule brings their strength nearly to that of inorganic acids. Thus, trifluoroacetic acid is a strong electrolyte and has the dissociation constant 0.59 [2].



The withdrawal of electrons by the fluorine atom from the radical R makes it so positive that there is the possibility of alkylation by esters of fluorine-substituted carboxylic acids.

The reaction of sodium p-chlorothiophenolate with methyl chlorodifluoroacetate was carried out as follows. We dissolved 5.8 g of p-chlorothiophenol in 10 ml of anhydrous alcohol and added a solution of sodium ethylate (0.92 g in 10 ml of alcohol). The alcohol was distilled off and the residue was dried in a vacuum. The resulting sodium p-chlorothiophenolate was mixed with 11.6 g of methyl chlorodifluoroacetate [3] and heated for nine hours at 90°. The reaction mixture was poured into a separatory funnel and shaken with 50 ml of ether and 50 ml of 1% sodium hydroxide. From the ether solution after distillation we obtained 5 g of p-chlorophenylmethyl sulfide (78.8% of the taken or 87.8% of the reacting p-chlorothiophenol). B.p. 75-76° (5 mm). The alkaline solution was acidified and shaken with ether. From the ether solution after removal of the chlorodifluoroacetic acid by shaking with a solution of sodium bicarbonate we obtained 0.6 g of p-chlorothiophenol. The bicarbonate solution was acidified, extracted with ether and the ether was distilled off. We obtained 1.4 g of chlorodifluoroacetic acid.

When we mixed 4.4 g of sodium phenolate with 11.6 g of methyl chlorodifluoroacetate, strong heating occurred and the mixture darkened. We heated for 15 hours at 90°. The reaction product was separated by the method described above. Yield of anisole 3.34 g (77.3% of the taken or 91% of the reacting phenol). We also isolated 3 g of chlorodifluoroacetic acid and 0.45 g of phenol.

The reaction of sodium p-chlorothiophenolate with ethyl trifluoroacetate was carried out in an analogous way. To dry sodium p-chlorothiophenolate obtained from 2.9 g of p-chlorothiophenol and 0.46 g of sodium in alcohol was added 8.5 g of ethyl trifluoroacetate. The mixture was heated for 20 hours at 70° and was diluted with ether. We filtered off 2.5 g (92.6%) of sodium trifluoroacetate. The ether was distilled off. p-Chlorophenylethyl sulfide was distilled in a vacuum. B.p. 125-126° (23 mm). Yield 2.8 g (82.4%).

For proof of the structure, the p-chlorophenylethyl sulfide was oxidized to the sulfone by a solution of hydrogen peroxide in acetic acid. M.p. 36-37°.

Found %: S 15.63, 15.76. $C_8H_9O_2SCl$. Calculated %: S 15.64.

p-Chlorophenylethyl sulfide was synthesized also from sodium p-chlorothiophenolate and ethyl iodide, and was then oxidized to the sulfone. M.p. 36-37°. A sample mixed with the other sulfone gave no melting point depression.

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Soviet Journals Available in Cover-to-Cover Translation

[illegible]

continued

Izv. AN SSSR, Otd. (Tekhn). N(auk): Met(ell). i top.	(see Met. i top.) Izvestiya Akademii Nauk SSSR: Seriya fizicheskaya	Bulletin of the Academy of Sciences of the USSR: Physical Series	1	1954
Izv. AN SSSR Ser. fiz(ich).	Izvestiya Akademii Nauk SSSR: Seriya geofizicheskaya	Sciences USSR: Geophysics Series	1	1954
Izv. AN SSSR Ser. geol.	Izvestiya Akademii Nauk SSSR: Seriya geologicheskaya	Sciences of the Academy of Sciences of the USSR: Geologic Series	1	1958
Kauch. i rez.	Kauchuk i rezina	Soviet Rubber Technology	18	1959
	Kinetika i kataliz	Kinetics and Catalysis	1	1959
	Koks i khimiya	Coke and Chemistry USSR	3	1960
Kolloidn. zh(urn).	Kolloidnyi zhurnal	Colloid Journal	14	1958
	Kristallografiya	Soviet Physics - Crystallography	2	1957
Metalov. i term. obrabot. metal.	Metallovedeniye i termicheskaya obrabotka metallov	Metals Science and Heat Treatment of Metals	6	1958
Met. i top.	Metallurgiya i topliva	Russian Metallurgy and Fuels	1	1960
OS	Mikrobiologiya	Microbiology	26	1957
	Optika i spektroskopiya	Optics and Spectroscopy	6	1959
	Pochvovedeniye	Soviet Soil Science	1	1958
	Priborostroeniye	Instrument Construction	1	1959
Pribory i tekhn. eksperimenta	Pribory i tekhnika eksperimenta	Instruments and Experimental Techniques	1	1959
Prikl. matem. i mekh.	Prikladnaya matematika i mekhanika	Applied Mathematics and Mechanics	1	1957
PTÉ	(see Pribory i tekhn. éks.)		1	1958
Radiolekh.	Problemy Severa	Problems of the North	12	1957
Radiolekh. i élektronika	Radioelekhnika	Radio Engineering	2	1957
	Stanki i instrument	Machines and Tooling	1	1959
	Steklo i keramika	Glass and Ceramics	13	1956
Stek. i keram.	Steklo i keramika	Glass and Ceramics	1	1956
Svaroch. proizvo.	Svarochnoe proizvodstvo	Welding Production	4	1959
Teor. veroyat. i prim.	Teoriya veroyatnostei i ee primeneniye	Theory of Probability and Its Applications	1	1956
	Tsvetnyye metally	Nonferrous Metals	1	1960
UFN	Uspekhi fizicheskikh Nauk	Soviet Physics - Uspekhi (partial translation)	1	1958
UMN	Uspekhi khimii	Russian Chemical Reviews	1	1960
Usp. fiz. nauk	Uspekhi matematicheskikh nauk	Russian Mathematical Surveys	15	1960
Usp. khim(ii)	(see UFN)			
Usp. matem. nauk	(see UMN)			
Usp. sovr. biol.	Uspekhi sovremennoi biologii	Soviet Physics - JETP	28	1955
Vest. mashinostroeniya	Vestnik mashinostroeniya	Russian Journal of Physical Chemistry	7	1959
Vop. gem. i per. krovi	Voprosy gematologii i perelivaniya krovi	Journal of Microbiology, Epidemiology and Immunobiology	1	1957
Vop. onk.	Voprosy onkologii	The Russian Journal of Inorganic Chemistry	1	1959
Vop. virusol.	Voprosy virusologii	Journal of General Chemistry USSR	19	1949
Zavodsk. laboratoriya	Zavodskaya laboratoriya	Journal of Applied Chemistry USSR	23	1950
ZhAKh Zh. anal(it). khimii	Zhurnal analiticheskoi khimii	Journal of Structural Chemistry	1	1960
ZhETF	Zhurnal éksperimental'noi i teoreticheskoi fiziki	Soviet Physics - Technical Physics	26	1956
Zh éksp(erim.) i teor. fiz.	Zh éksp(erim.) i teor. fiz.	Zhurnal tekhnicheskoi fiziki		
ZhFKh Zh. fiz. khimii	Zhurnal fizicheskoi khimii	Zhurnal vysshei nervnoi deyatel'nosti (im. I. P. Pavlova)		
ZhMET Zh(urn). mikrobiol. i epidemiol. i immunobiol.	Zhurnal mikrobiologii, epidemiologii i immunobiologii			
ZhNKh Zh(urn). neorgan(ich). khim(ii)	Zhurnal neorganicheskoi khimii			
ZhOKh Zh(urn). obshch(ei) khimii	Zhurnal obshchei khimii			
ZhPKh Zh(urn). prikl. khimii	Zhurnal prikladnoi khimii			
ZhSKh Zh(urn). strukt. khimii	Zhurnal strukturnoi khimii			
ZhTF Zh(urn). tekhn. fiz.	Zhurnal tekhnicheskoi fiziki			
Zh(urn). vyssh. nervn. deyat. (im. Pavlova)	Zhurnal vysshei nervnoi deyatel'nosti (im. I. P. Pavlova)			

*Sponsoring organization. Translation through 1960 issues is a publication of Pergamon Press.

SIGNIFICANCE OF ABBREVIATIONS MOST FREQUENTLY ENCOUNTERED IN SOVIET PERIODICALS

FIAN	Phys. Inst. Acad. Sci. USSR.
GDI	Water Power Inst.
GITI	State Sci.-Tech. Press
GITTL	State Tech. and Theor. Lit. Press
GONTI	State United Sci.-Tech. Press
Gosenergoizdat	State Power Press
Goskhimizdat	State Chem. Press
GOST	All-Union State Standard
GTTI	State Tech. and Theor. Lit. Press
IL	Foreign Lit. Press
ISN (Izd. Sov. Nauk)	Soviet Science Press
Izd. AN SSSR	Acad. Sci. USSR Press
Izd. MGU	Moscow State Univ. Press
LEIIZhT	Leningrad Power Inst. of Railroad Engineering
LET	Leningrad Elec. Engr. School
LETI	Leningrad Electrotechnical Inst.
LETIIZhT	Leningrad Electrical Engineering Research Inst. of Railroad Engr.
Mashgiz	State Sci.-Tech. Press for Machine Construction Lit.
MEP	Ministry of Electrical Industry
MES	Ministry of Electrical Power Plants
MESEP	Ministry of Electrical Power Plants and the Electrical Industry
MGU	Moscow State Univ.
MKhTI	Moscow Inst. Chem. Tech.
MOPI	Moscow Regional Pedagogical Inst.
MSP	Ministry of Industrial Construction
NII ZVUKSZAPIOI	Scientific Research Inst. of Sound Recording
NIKFI	Sci. Inst. of Modern Motion Picture Photography
ONTI	United Sci.-Tech. Press
OTI	Division of Technical Information
OTN	Div. Tech. Sci.
Stroizdat	Construction Press
TOE	Association of Power Engineers
TsKTI	Central Research Inst. for Boilers and Turbines
TsNIEL	Central Scientific Research Elec. Engr. Lab.
TsNIEL-MES	Central Scientific Research Elec. Engr. Lab. - Ministry of Electric Power Plants
TsVTI	Central Office of Economic Information
UF	Ural Branch
VIESKh	All-Union Inst. of Rural Elec. Power Stations
VNIIM	All-Union Scientific Research Inst. of Metrology
VNIIZhDT	All-Union Scientific Research Inst. of Railroad Engineering
VTI	All-Union Thermotech. Inst.
VZEI	All-Union Power Correspondence Inst.

Note: Abbreviations not on this list and not explained in the translation have been transliterated, no further information about their significance being available to us. - Publisher.



